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CERTIFICATE

This certificate is issued in support of an application for Patent registration in a country outside New Zealand pursuant to the Patents Act 1953 and the Regulations thereunder.

I hereby certify that annexed is a true copy of the Provisional Specification as filed on 17 September 2002 with an application for Letters Patent number 521436 made by AUCKLAND UNISERVICES LIMITED; THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY.

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PROVISIONAL SPECIFICATION

DNA-TARGETED BENZOTRIAZINE 1,4-DIOXIDES AND THEIR USE IN CANCER THERAPY

We, **AUCKLAND UNISERVICES LIMITED**, a New Zealand company, of Level 10, 70 Symonds Street, Auckland, New Zealand and **THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY**, of 900 Welch Road, Suite 350, Palo Alto, CA 94304 1850, United States of America do hereby declare this invention to be described in the following statement:

PT0415130

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DNA-TARGETED BENZOTRIAZINE 1,4-DIOXIDES AND THEIR USE IN CANCER THERAPY

REFERENCE TO GOVERNMENT CONTRACT

The invention described herein was made in the course of work under grant or contract from the United States Department of Health and Human Services. The United States Government has certain rights to this invention.

TECHNICAL FIELD

The present invention relates to DNA-targeted 1,2,4-benzotriazine-1,4-dioxides and related analogues, to their preparation, and to their use as hypoxia-selective drugs and radiosensitizers for cancer therapy, both alone or in combination with radiation and/or other anticancer drugs.

BACKGROUND TO THE INVENTION

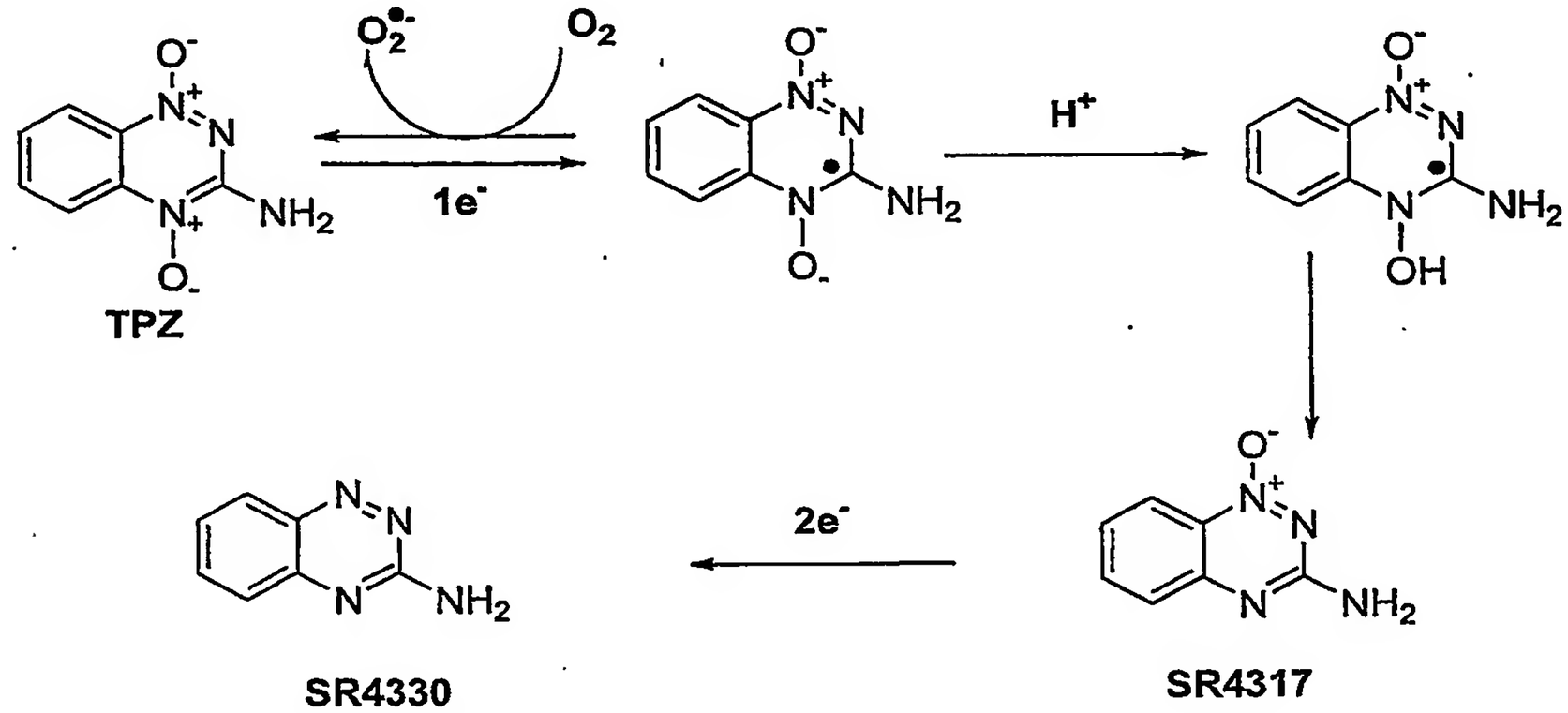
It has been established that many human tumors contain a significant hypoxic fraction of cells (Kennedy et al., *Int. J. Radiat. Oncol. Biol. Phys.*, **1997**, 37, 897-905; Movsas et al., *Urology*, **1999**, 53, 11-18). The presence of hypoxic cells arises because of chaotic growth and an inefficient microvasculature system within the tumor, which leads to large intercapillary distances and variable blood flow. Reduction of oxygen tension in tumors leads to radioresistence. This reduction of oxygen tension causes up to a three-fold increase in radiation dose being required to kill anoxic tumor cells. A link has been identified between the presence of tumor hypoxia and failure of local control by radiation therapy (Brizel et al., *Radiother. & Oncol.*, **1999**, 53, 113-117). This phenomenon of tumor hypoxia has been exploited in the development of a class of anticancer agents termed 'bioreductive drugs' (Brown et al., Semin. Radiat. Oncol., 1966, 6, 22-36; Denny et al., *Br. J. Cancer*, **1996**, 74 (Suppl. XXVII) 32-38; Stratford & Workman, *Anti-Cancer Drug Des.*, **1998**, 13, 519-528). These agents are selectively active against hypoxic cells in tumors by targeting the DNA of these cells. The agents cause irreversible damage to the DNA of the tumor cells, thereby causing the destruction and breakdown of the tumor.

Tirapazamine (TPZ, 3-amino-1,2,4-benzotriazine 1,4-dioxide) is a bioreductive agent (Kelson et al., *Anti-Cancer Drug Des.*, **1998**, 13, 575-592; Lee et al., WO 9104028,

April 1991) and is undergoing clinical trials in combination with radiotherapy and various chemotherapeutics, notably cisplatin (Denny & Wilson, *Exp. Opin. Invest. Drugs*, **2000**, 9, 2889-2901).

TPZ is activated by one electron reductases (Patterson et al., *Anti-Cancer Drug Des.* **1998** 13, 541-573; Denny & Wilson, *Exp. Opin. Invest. Drugs*, **2000**, 9, 2889-2901) to form a radical anion (Scheme A). This TPZ radical anion may be oxidized back to TPZ by molecular oxygen under aerobic conditions.

Scheme A.



Under hypoxic conditions the radical or species ultimately derived from TPZ can interact with DNA, although the exact mechanism is unclear (Jones et al., *Cancer Res.*, **1996**, 56, 1584-1590; Daniels et al., *Chem. Res. Toxicol.*, **1998**, 11, 1254-1257; Hwang et al., *Biochem.*, **1999**, 38, 14248-14255). TPZ causes DNA double-strand breaks under anoxic conditions (Jones et al., *Cancer Res.*, **1996**, 56, 1584-1590) and these results correlate with cytotoxicity (Dorie et al., *Neoplasia,* **1999**, 1, 461-467). Reversible one-electron reduction of TPZ that gives rise to a reactive radical species that is thought to be the basis for selective toxicity to hypoxic cells. Two electron reduction of TPZ or further reduction of the TPZ radical produces the metabolite 1-oxide (SR 4317) and further reduction gives the nor-oxide (SR 4330) (Baker et al., *Cancer Res.*, **1988**, 48, 5947-5952; Laderoute & Rauth, *Biochem Pharmacol.*, **1986**, 35, 3417-3420) (Scheme A). The metabolites (SR 4317) and (SR 4330) are both inactive under aerobic or hypoxic conditions.

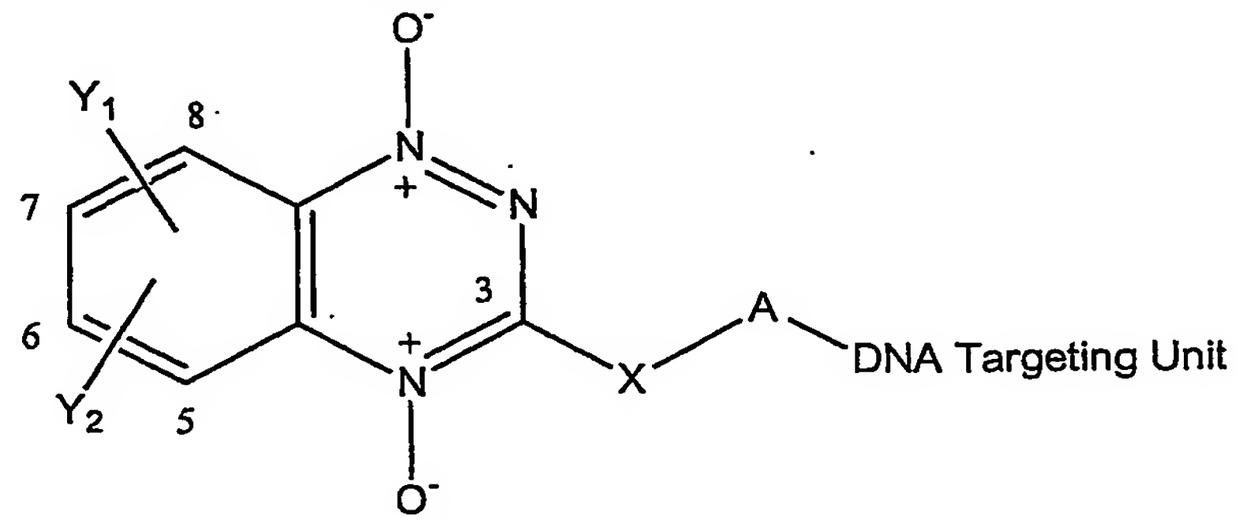
It is also known that reactive species can be effectively targeted to DNA by attachment to DNA-affinic carriers. Thus, the intrinsic cytotoxicities and *in vivo*

potencies of aniline mustards can be significantly increased (up to 100-fold), and the usual dependence of cytotoxicity on mustard reactivity lowered, by targeting to DNA via a 9-aminoacridine carrier (Gourdie et al., *J. Med. Chem.*, **1990**, 33, 1177-1185). DNA alkylation patterns can also be significantly altered (Prakash et al., *Biochem.*, **1990**, 29, 9799-9807; Boritzki et al., *Chem. Res. Toxicol.*, **1994**, 7, 41-46). Alkylation of DNA by DNA-targeted compounds is more rapid than with the corresponding untargeted compounds (O'Connor et al., *Chem.-Biol. Int.*, **1992**, 85, 1-14). However, the extent of DNA binding needs to be carefully adjusted to achieve effective targeting without significantly compromising the transport/diffusion properties (Hicks et al., *J. Pharmacol. Exp. Therapeut.* **2001**, 297,1088-1098; Hicks et. al, *Brit. J. Cancer*. **1997**, 76, 894-903). Binding ability can be varied by alteration of both the chromophore and substituents on the DNA targeted compound (Palmer et al., *J. Med. Chem.*, **1988**, 31, 707-712).

It is an object of the present invention to utilize DNA-affinic carriers in combination with benzotriazine 1,4-dioxides to target DNA for cancer therapy purposes, or to at least provide the public with a useful choice.

DISCLOSURE OF THE INVENTION

In a first aspect, the present invention provides a compound of Formula I,



I

wherein

Y_1 and Y_2 may each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, $NR^2{}_2$ or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X may represent NH, NMe, CH_2, SO, SO_2, or O;

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, $NR^3{}_2$, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, $NR^5{}_2$ or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of $>10^3$ M^{-1} at an ionic strength of 0.01 M at 20 °C,

or a pharmacologically acceptable salt thereof.

The definition of the DNA targeting unit above refers to double-stranded random-sequence DNA. An example of such double-stranded random-sequence DNA is DNA extracted from calf thymus.

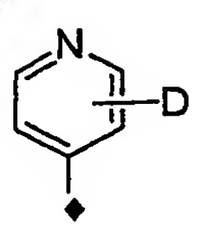
A preferred compound of Formula I is one in which X is NH or CH_2.

A further preferred compound of Formula I is one in which Y_1 and Y_2 each represent H.

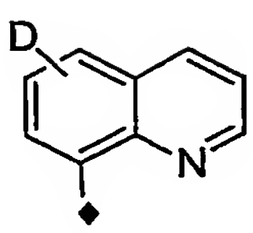
A further preferred compound of Formula I is one in which Y_1 represents OMe

A preferred embodiment of Formula I are compounds wherein A is selected from $-(CH_2)_6NH-$, $-(CH_2)_3NH(CH_2)_3NHCO-$, $-(CH_2)_3NMe(CH_2)_3NHCO-$, $-(CH_2)_3NH-$, $-(CH_2)_2NH(CH_2)_2NHCO-$ or $-(CH_2)_2NMe(CH_2)_2NHCO-$.

A further preferred embodiment of Formula I are compounds wherein the DNA-targeting unit is selected from one of formulae **II- XVI**,



II



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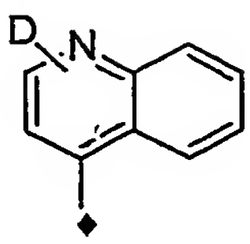

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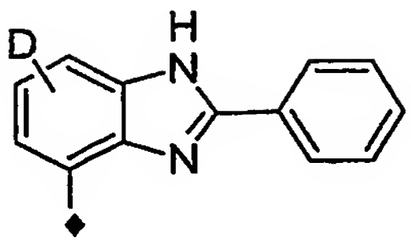
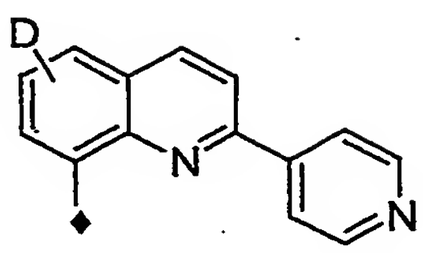
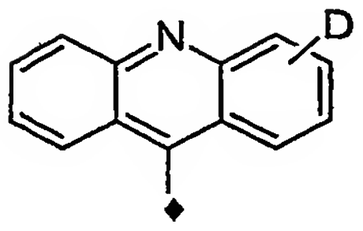


V



VI



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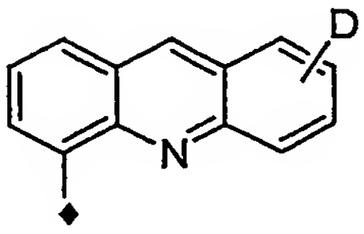
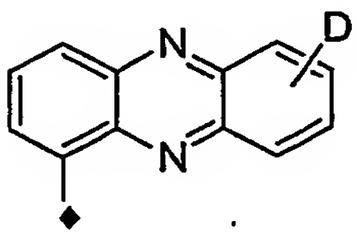


VIII



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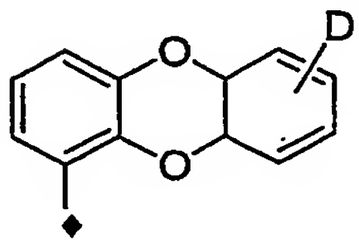
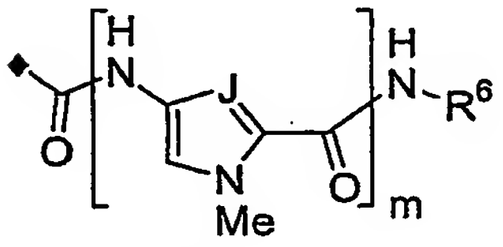
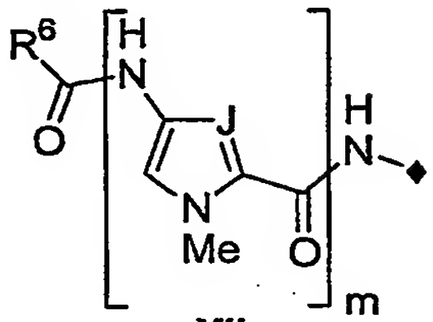


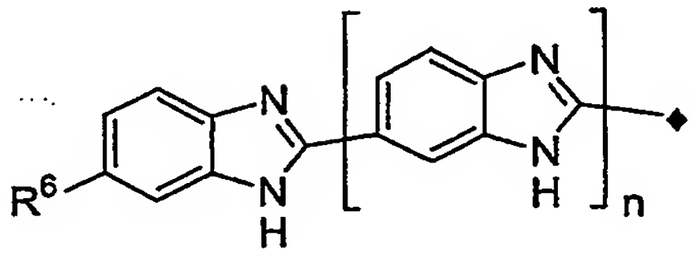
X



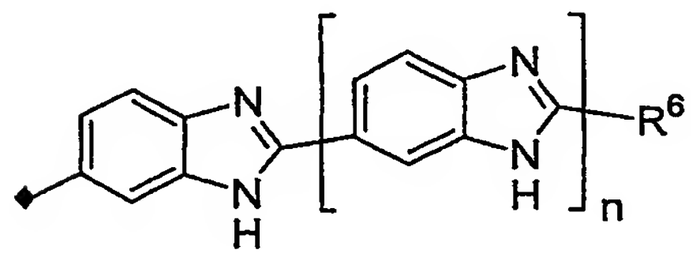
XI



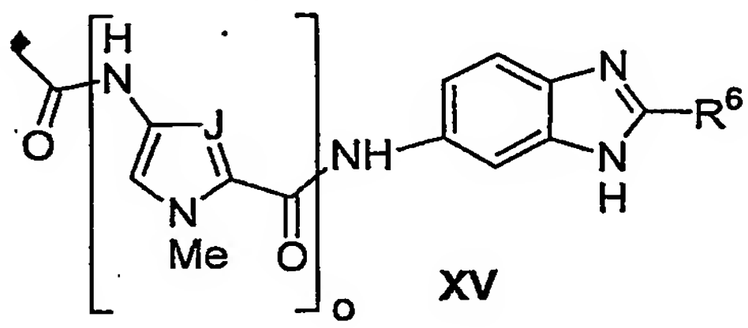
XII



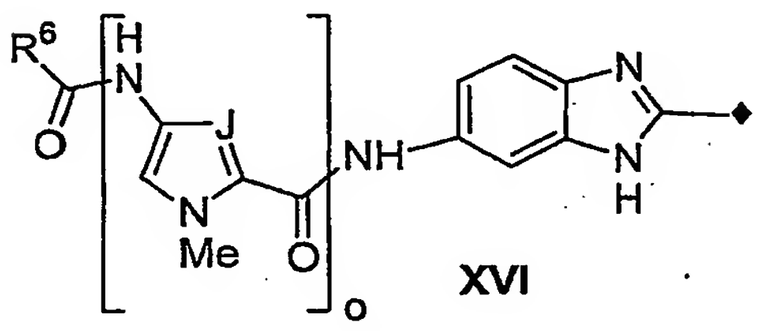
XIII



XIV



XV



XVI

wherein in structures **XI-XVI** R^6 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 NO_2, NH_2, NHR^7, NR^7R^7, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$;

R^6 may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7, NH_2, NHR^7, NR^7R^7, SH, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or

S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8, NH_2, NHR^8, $NR^8{}_2$ or $N(OH)R^8$ wherein each R^8 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

D may represent up to four of the following groups as substituents at any available ring carbon position; H, R^9, hydroxy, alkoxy, halogen, NO_2, NH_2, NHR^9, $NR^9{}_2$, SH, SR^9, SO_2R^9, CF_3, CN, CO_2H, CO_2R^9, CHO, COR^9, $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, wherein each R^9 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10}, NH_2, NHR^{10}, $NR^{10}{}_2$ or $N(OH)R^{10}$ wherein each R^{10} may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

and wherein any available ring carbon position of formulae **II - XVI** may also be optionally replaced by –N- when the valency and configuration of the formula allows,

the point of attachment of formulae **II- XVI** to the A group defined above is represented by ♦; and

wherein in formulae **XI, XII,** , m may be selected from 2, 3 or 4, and

wherein in formulae **XI, XII, XV** and **XVI,** J may be selected from CH or N;

and wherein in formulae **XIII** and **XIV** n may be selected from 0, 1 or 2;

and wherein in formulae **XV** and **XVI** o may be selected from 1 and 2.

A preferred embodiment of formula I is one in which the DNA targeting unit is selected from one of formulae IV, V, VI, VII, VIII, or IX.

A preferred embodiment of formula I is one in which D of the DNA targeting unit of Formulae II - X is H or Me.

Further preferred compounds of formula I include the following

wherein X is NH-, Y is H, A is $-(CH_2)_6NH-$, the DNA targeting unit represents formula

VII and D is H;

wherein X is NH-, Y is H, A is $-(CH_2)_3NH(CH_2)_3NHCO-$, the DNA targeting unit represents formula VIII and D is H;

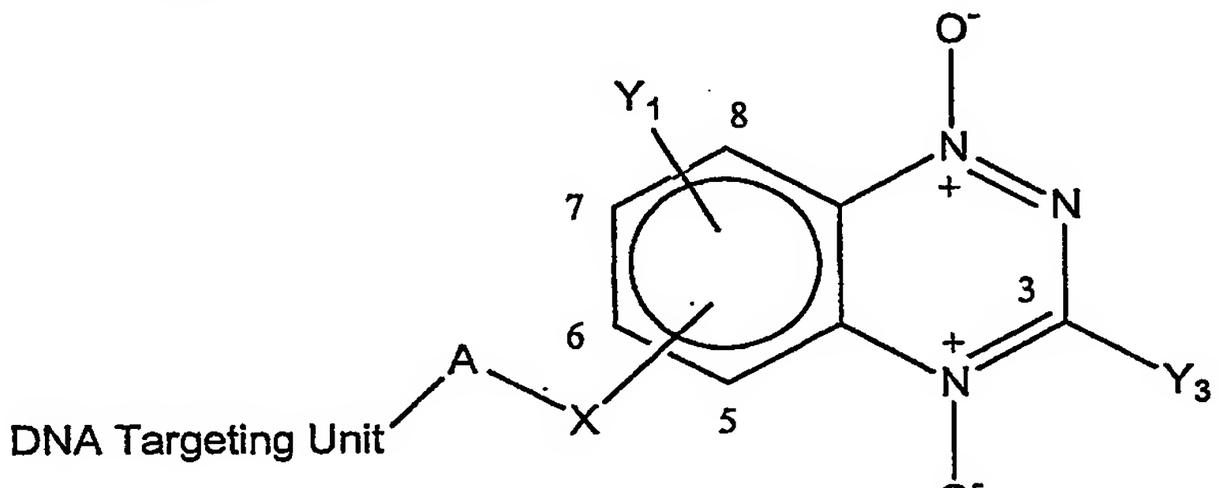
wherein X is NH-, Y is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula VIII and D is Me;

wherein X is NH-, Y is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is Me; and

wherein X is NH-, Y is H, A is $-(CH_2)_3NH-$, the DNA targeting unit represents formula IV and D is 7-Cl.

In a second aspect, the present invention provides a compound of Formula I',



I'

wherein

Y_1 may represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

Y_3 may be selected from the following groups halo, H, R, OR, NH_2, NHR, NR_2, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino,

imidazolyl, alkylpiperazinyl, morpholino;

wherein each R of groups Y_1 and Y_3 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X may represent NH, NMe, CH_2, SO, SO_2, or O;

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2 or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{2-12} alkyl chain may be optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of $>10^3$ M^{-1} at an ionic strength of 0.01 M at 20 °C,

or a pharmacologically acceptable salt thereof.

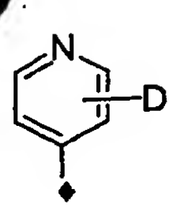
The definition of the DNA targeting unit above refers to double-stranded random-sequence DNA. An example of such double-stranded random-sequence DNA is DNA extracted from calf thymus.

A preferred compound of Formula I′ is one in which X is O, NH or CH_2.

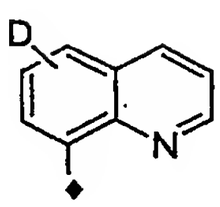
A further preferred compound of Formula I′ is one in which Y_1 represents H.

A preferred embodiment of Formula I′ are compounds wherein A is selected from $-(CH_2)_6NH-$, $-(CH_2)_3NH(CH_2)_3NHCO-$, $-(CH_2)_3NMe(CH_2)_3NHCO-$, $-(CH_2)_3NH-$, $-(CH_2)_2NH(CH_2)_2NHCO-$ or $-(CH_2)_2NMe(CH_2)_2NHCO-$.

A further preferred embodiment of Formula I′ are compounds wherein the DNA-targeting unit is selected from one of formulae **II- XVI**,



II



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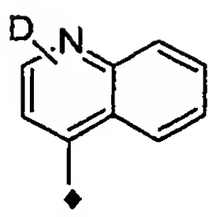

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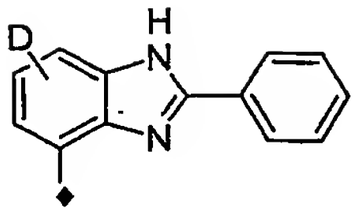
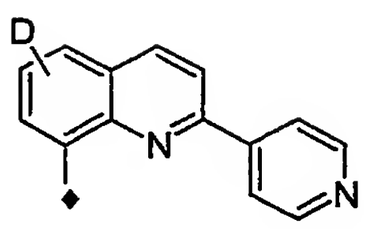
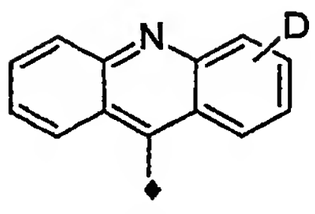


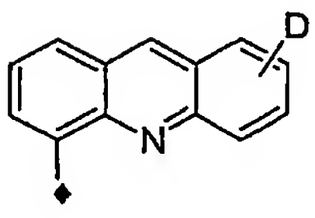
V



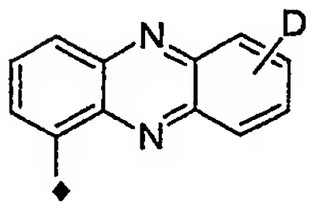
VI



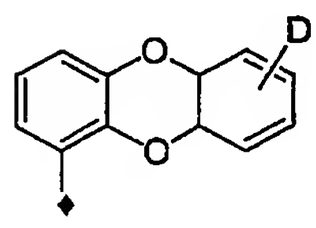
VII



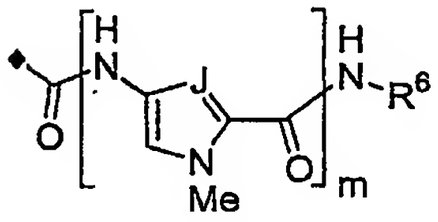
VIII



IX



X



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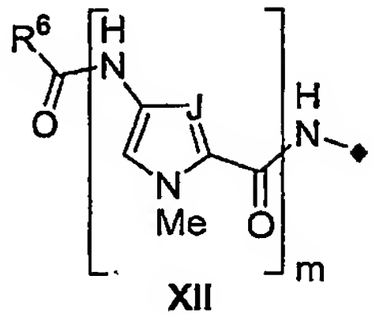
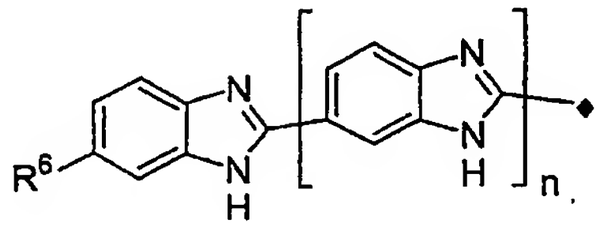
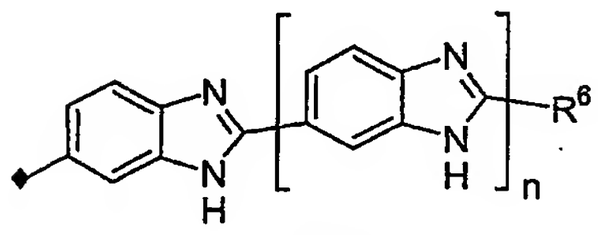


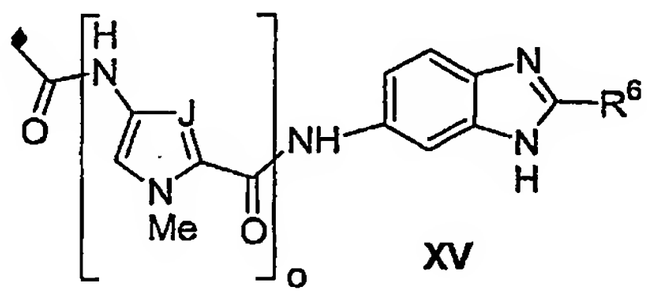
XII



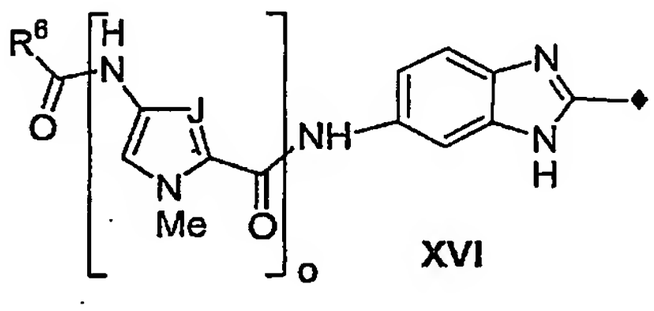
XIII



XIV



XV



XVI

wherein in structures **XI - XVI** R^6 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 NO_2, NH_2, NHR^7, NR^7R^7, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$;

R^6 may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7, NH_2, NHR^7, NR^7R^7, SH, SR^7, imidazolyl, R^7-piperazinyl, morpholino, SO_2R^7, CF_3, CN, CO_2H, CO_2R^7, CHO, COR^7, $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8, NH_2, NHR^8, $NR^8{}_2$ or $N(OH)R^{98}$ wherein each R^8 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

D may represent up to four of the following groups as substituents at any available ring carbon position; H, R^9, hydroxy, alkoxy, halogen, NO_2, NH_2, NHR^9, $NR^9{}_2$, SH, SR^9, SO_2R^9, CF_3, CN, CO_2H, CO_2R^9, CHO, COR^9, $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, wherein each R^9 independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10}, NH_2, NHR^{10}, $NR^{10}{}_2$ or $N(OH)R^{10}$ wherein each R^{10} may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

and wherein any available ring carbon position of formulae **II- XVI** may also be optionally replaced by –N- when the valency and configuration of the formula allows, the point of attachment of formulae **II- XVI** to the A group defined above is represented by ♦; and

wherein in formulae **XI** and **XII**, m may be selected from 2, 3 or 4,

and wherein in formulae **XI, XII, XV or XVI** J may be selected from CH or N; and

wherein in formulae **XIII** and **XIV** n may be selected from 0, 1 or 2, and

wherein in formulae **XV** and **XVI** o may be selected from 1 or 2.

A preferred embodiment of formula I′ is one in which the DNA targeting unit is selected from one of formulae III - IX.

A preferred embodiment of formula I′ is one in which D of the DNA targeting unit of Formulae II – X is H or Me.

Preferred compounds of formula I′ include the following

wherein X is NH-, Y is H, A is $-(CH_2)_3NH(CH_2)_3NHCO-$, the DNA targeting unit represents formula V and D is H;

wherein X is NH-, Y is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula V and D is H;

wherein X is NH-, Y is H, A is$-(CH_2)_3NH(CH_2)_3NHCO-$, the DNA targeting unit represents formula VI and D is H;

wherein X is NH-, Y is H, A is$-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula VI and D is H;

wherein X is NH-, Y is H, A is$-(CH_2)_3NH(CH_2)_3NHCO-$, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y is H, A is$-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula VIII and D is H;

wherein X is NH-, Y is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula VIII and D is Me;

wherein X is NH-, Y is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is H, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is Me;

wherein X is NH-, Y is H, A is $-(CH_2)_3NH-$, the DNA targeting unit represents formula IV and D is 7-Cl.

In a third aspect the invention provides for the use in a method of therapy for treating cancers including the step of administering a compound of Formula I as defined above or a compound of Formula I′ as defined above or a mixture thereof in a therapeutically effective amount to tumour cells in a subject.

Preferably the tumour cells are in a hypoxic environment.

It is preferred that the method of therapy further includes the step of administering radiotherapy to the tumor cells before, during or after the administration of the compound of Formula I as defined above or a compound of Formula I′ as defined above or a mixture thereof to the tumour cells.

It is preferred that the method of therapy further includes the step of administering one or more chemotherapeutic agents to the tumor cells before, during or after the administration of the compound of Formula I as defined above or a compound of Formula I′ as defined above or a mixture thereof to the tumour cells.

While these compounds will typically be used in cancer therapy of human subjects, they may be used to target tumor cells in other warm blooded animal subjects such as other primates, farm animals such as cattle, and sports animals and pets such as horses, dogs, and cats.

A "therapeutically effective amount", is to be understood as an amount of a compound of Formula I as defined above or a compound of Formula I′ as defined above or a mixture thereof that is sufficient to show benefit to a patient. The actual amount, rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment is within the responsibility of general practitioners and other medical doctors..

A hypoxic environment is to be understood as either an *in vitro* or *in vivo* environment having a poorer blood supply and lower oxygen tension than normal tissues.

It is to be understood that the compound of Formula I or Formula I′ may be administered alone or in combination with other chemotherapeutic agents or treatments, especially radiotherapy, either simultaneously or sequentially dependent upon the condition to be treated.

Preferred chemotherapeutic agents may be selected from:

Cisplatin or other platinum-based derivatives,
Temozolomide or other DNA methylating agents,
Cyclophosphamide or other DNA alkylating agents,
Doxorubicin, mitoxantrone, camptothecin or other topoisomerase inhibitors,
Methotrexate, gemcitabine or other antimetabolites.

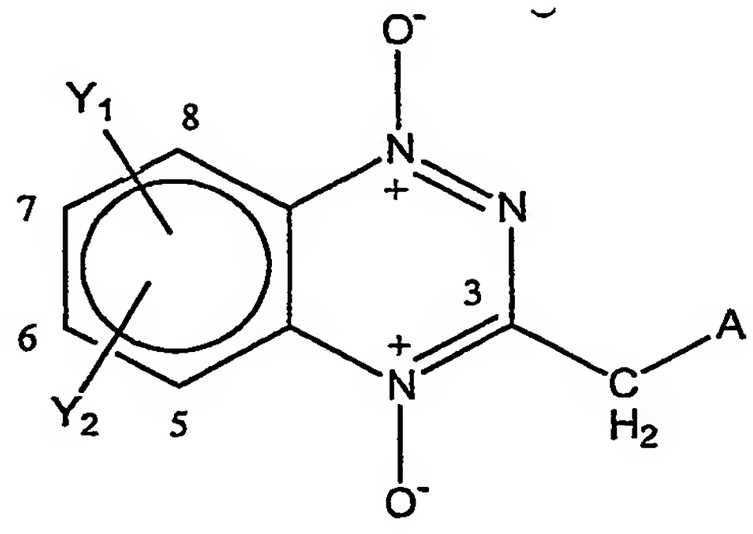
In a fourth aspect of the present invention there is provided a pharmaceutical composition including a therapeutically effective amount of a compound of formula I or compound of formula I′ or a mixture thereof, a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser.

The pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, such as cutaneous, subcutaneous, or intravenous injection.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvent. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. A capsule may comprise a solid carrier such as gelatin.

For intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has a suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride injection, Ringer's injection, Lactated Ringer's injection. Preservatives, stabilisers, buffers antioxidants and/or other additives may be included as required.

In a fifth aspect of the present invention there is provided a method of making a compound of formula XVII



XVII

wherein

Y_1 and Y_2 may each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

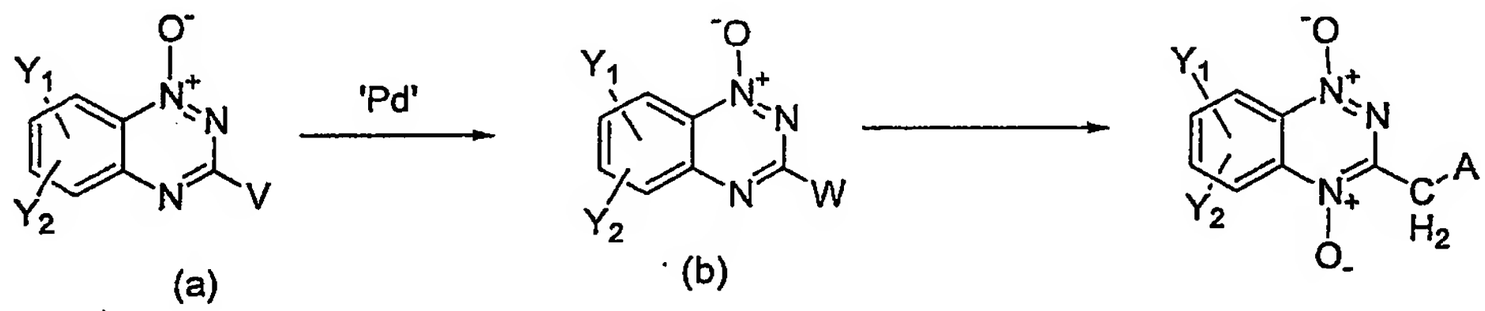
R may also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

or a pharmacologically acceptable salt thereof,

including the step of coupling a compound (a) using a palladium reagent to form compound (b) which may then be converted into a compound of XVII as defined above;



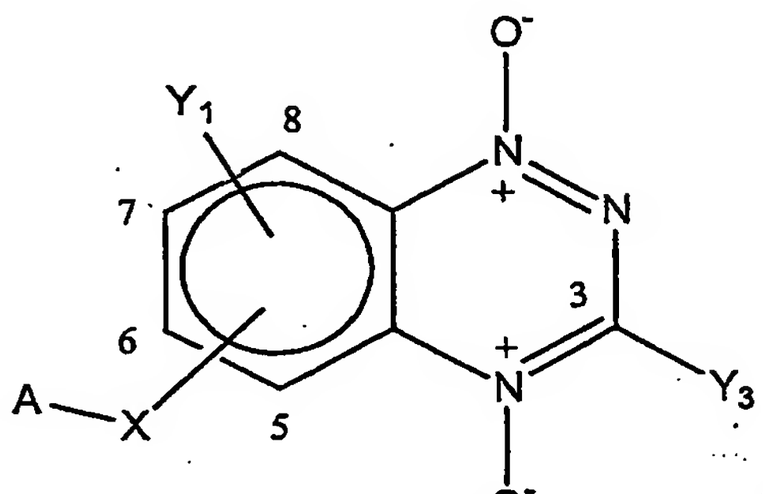
(a) (b) **XVII**

wherein in compound (a)

V is halogen which may be selected from Cl, Br or I and Y_1, Y_2 are as defined above; and wherein in compound (b) Y_1, Y_2 are as defined above, W may be selected from an optionally substituted

C_{1-12}alkyl, optionally substituted C_{2-12}alkenyl, and optionally substituted C_{2-12}alkynyl group, wherein the optional substituents may be selected from halo, OH, OR^6, NO_2, NH_2, NHR^6, NR^6R^6, SH, SR^6, imidazolyl, R^6-piperazinyl, morpholino, SO_2R^6, CF_3, CN, CO_2H, CO_2R^6, CHO, COR^6, $CONH_2$, $CONHR^6$, $CONR^6R^6$, wherein each R^6 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^7, NR^7_2 or $N(OH)R^7$ wherein each R^7 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH.

In a sixth aspect of the present invention there is provided a method of making a compound of formula XVII'



XVII'

wherein Y_1 may represent at one or more of the available carbons 5-8 on the benzo ring the following groups:
halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

Y_3 may be selected from the following groups H, R, OR, NH_2, NHR, NR_2, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino

wherein each R of groups Y_1 and Y_3 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

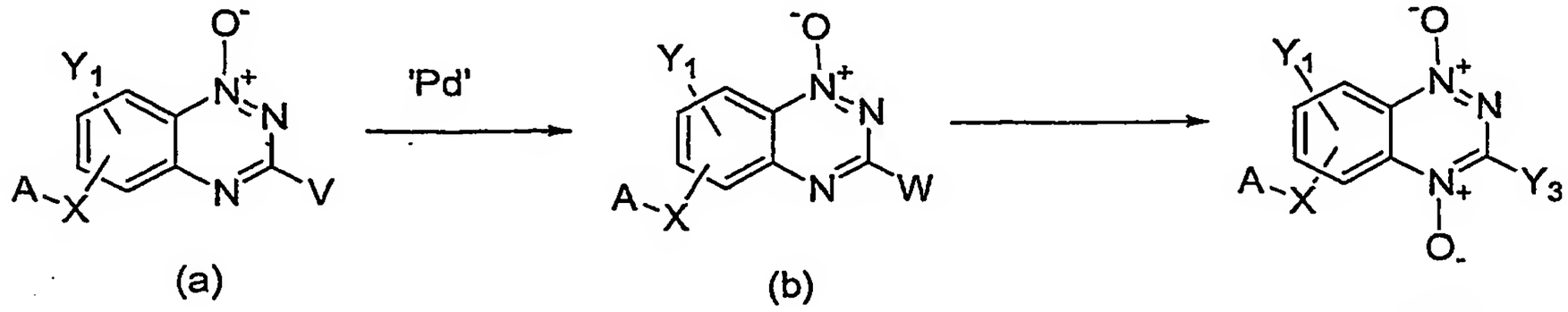
wherein each R^1 is independently selected from an optionally substituted

C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2 NR^2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X may represent NH, NMe, CH_2, SO, SO_2, or O;

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3 NR^3 or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, wherein each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, $NR^5{}_2$ or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

or a pharmacologically acceptable salt thereof;
including the steps of coupling a compound (a) using a palladium reagent to form compound (b) which may then be converted into a compound of XVII' as defined above;

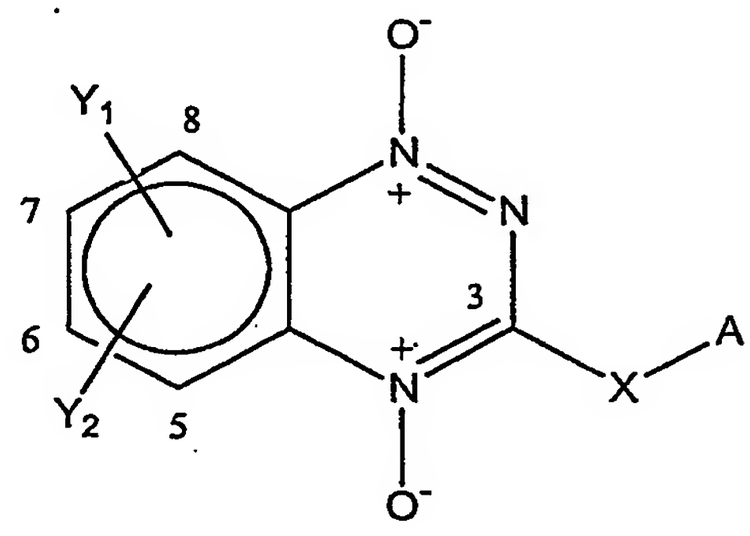


(a) (b) XVII'

wherein in compound (a)
V is halogen which may be selected from Cl, Br or I; Y_1, X and A are as defined above;
and wherein in compound (b) Y_1, X and A are as defined above,
W may be selected from an optionally substituted

C_{1-12}alkyl, optionally substituted C_{2-12}alkenyl, and optionally substituted C_{2-12}alkynyl group, wherein the optional substituents may be selected from halo, OH, OR^6, NO_2, NH_2, NHR^6, NR^6R^6, SH, SR^6, imidazolyl, R^6-piperazinyl, morpholino, SO_2R^6, CF_3, CN, CO_2H, CO_2R^6, CHO, COR^6, $CONH_2$, $CONHR^6$, $CONR^6R^6$, wherein each R^6 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^7, $NR^7{}_2$ or $N(OH)R^7$ wherein each R^7 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH.

In a seventh aspect of the present invention there is provided a compound of formula XVIII



XVIII

wherein

Y_1 and Y_2 may each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are

each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

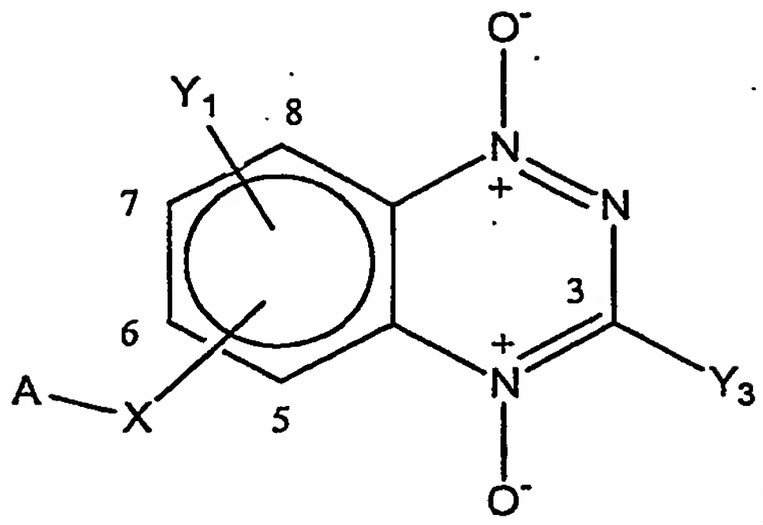
wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X may represent NH, NMe, CH_2, SO, SO_2, or O;

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH;

or a pharmacologically acceptable salt thereof.

In an eighth aspect of the present invention there is provided a compound of formula XVII'



XVII'

wherein

Y_1 may represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

Y_3 may be selected from the following groups H, R, OR, NH_2, NHR, NR_2, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino

wherein each R of groups Y_1 and Y_3 may be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R may also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X may represent NH, NMe, CH_2, SO, SO_2, or O;

A may represent an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2 or $N(OH)R^3$ wherein each R^3 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain may be optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 may be independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

wherein X may represent NH, NMe, CH_2, SO, SO_2, or O;

or a pharmacologically acceptable salt thereof.

In a ninth aspect of the present invention there is provided a method of making a compound of Formula I defined above including the steps of

1 preparing a compound of Formula XVIII as defined above
2 coupling the compound of Formula XVIII with a DNA targeting agent as defined above to provide a compound of Formula I.

In a tenth aspect of the present invention there is provided a method of making a compound of Formula I′ defined above including the steps of

1 preparing a compound of Formula XVII′ as defined above
2 coupling the compound of Formula XVII′ with a DNA targeting agent as defined above to provide a compound of Formula I′.

It is to be recognised that certain compounds of the present invention may exist in one or more different enantiomeric or diastereomeric forms. It is to be understood that the enantiomeric or diasteriomeric forms are included in the above aspects of the invention.

The term halo or halogen group used throughout the specification is to be taken as meaning a fluoro, chloro, bromo or iodo group.

The term pharmaceutically acceptable salt used throughout the specification is to be taken as meaning any acid or base derived salts formed from hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, isoethonic acids and the like and potassium carbonate sodium or potassium hydroxide ammonia, triethylamine, triethanolamine and the like.

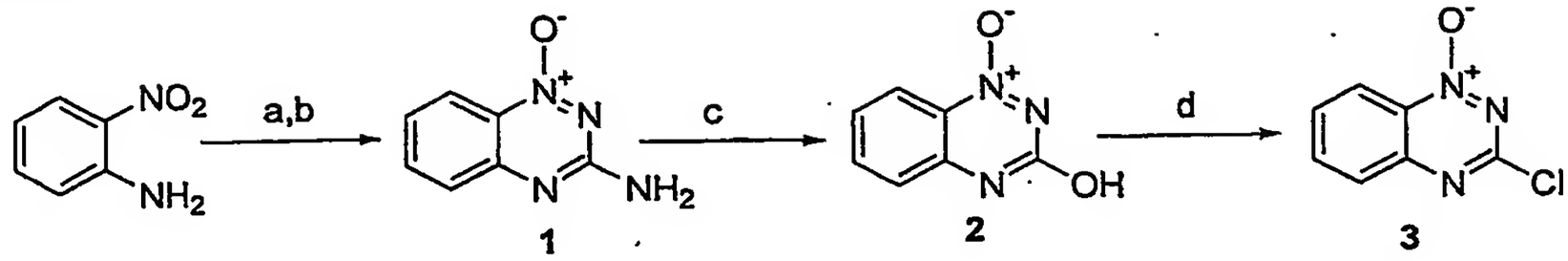
Further aspects of the present invention will become apparent from the following description given by way of example only and with reference to the accompanying synthetic schemes.

DETAILED DESCRIPTION OF THE INVENTION

Methods for preparing compounds of Formula I of the invention.

3-Chloro-1,2,4-benzotriazine 1-oxide (3) was readily synthesised from 2-nitroaniline in 3 steps (50% yield) (Scheme 1). Preparation of the diamine **4** can be achieved as shown in Scheme 2. Coupling of chloride **3** with the monoprotected diamine **4**, readily prepared in 85% yield from the 6-aminohexan-1-ol, gave carbamate **5** as illustrated in Scheme 3. Reaction of **5** with MCPBA in DCM gives 1,4-dioxide **6** in 39% yield and recovered starting material **5** (50%). This represents a departure from known methods (Lee et al, US Patent 5616584, April, 1997) that use trifluoroperacetic acid as the oxidant. Cleavage of the 1,4-dioxide carbamate **6** with HCl in MeOH gave 1,4-dioxide **7** in good yield.

Scheme 1



Reagents:

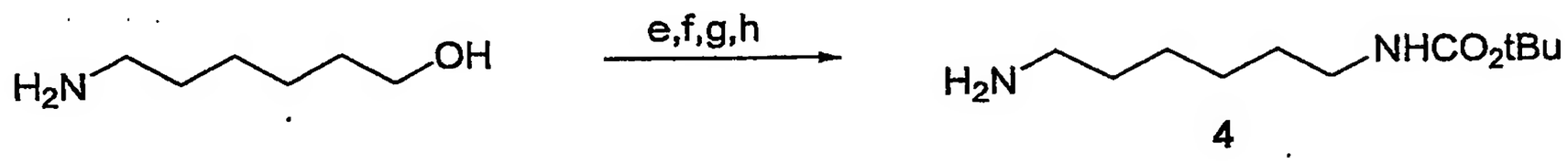
a) NH_2CN, HOAc, HCl;

b) NaOH;

c) HCl, $NaNO_2$, 49% from nitroaniline;

d) $POCl_3$, $PhNMe_2$, 59%

Scheme 2



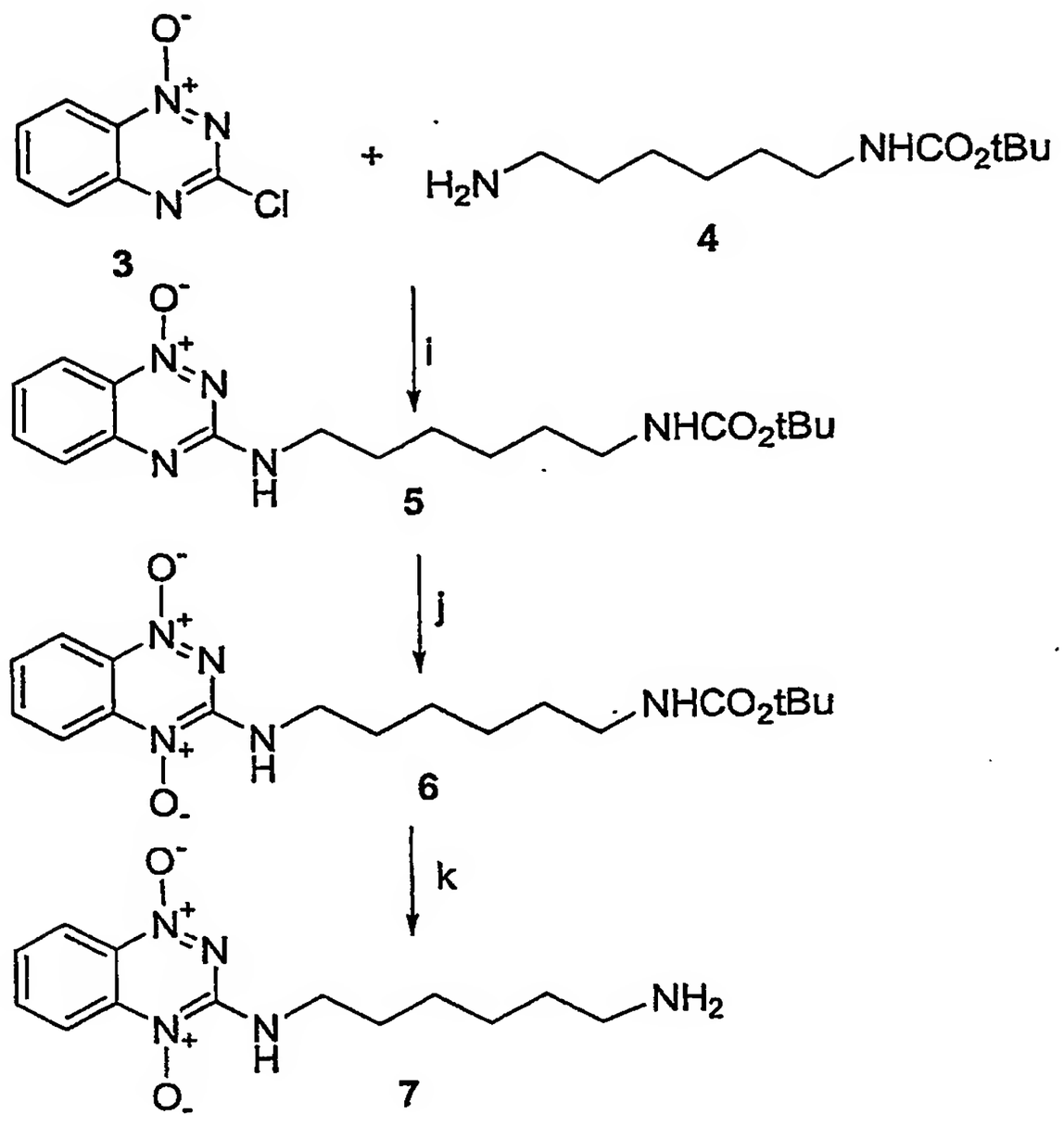
Reagents:

e) BOC_2O, DCM;

f) MsCl, Et_3N, DCM;

g) NaN_3, DMF.

Scheme 3



Reagents:

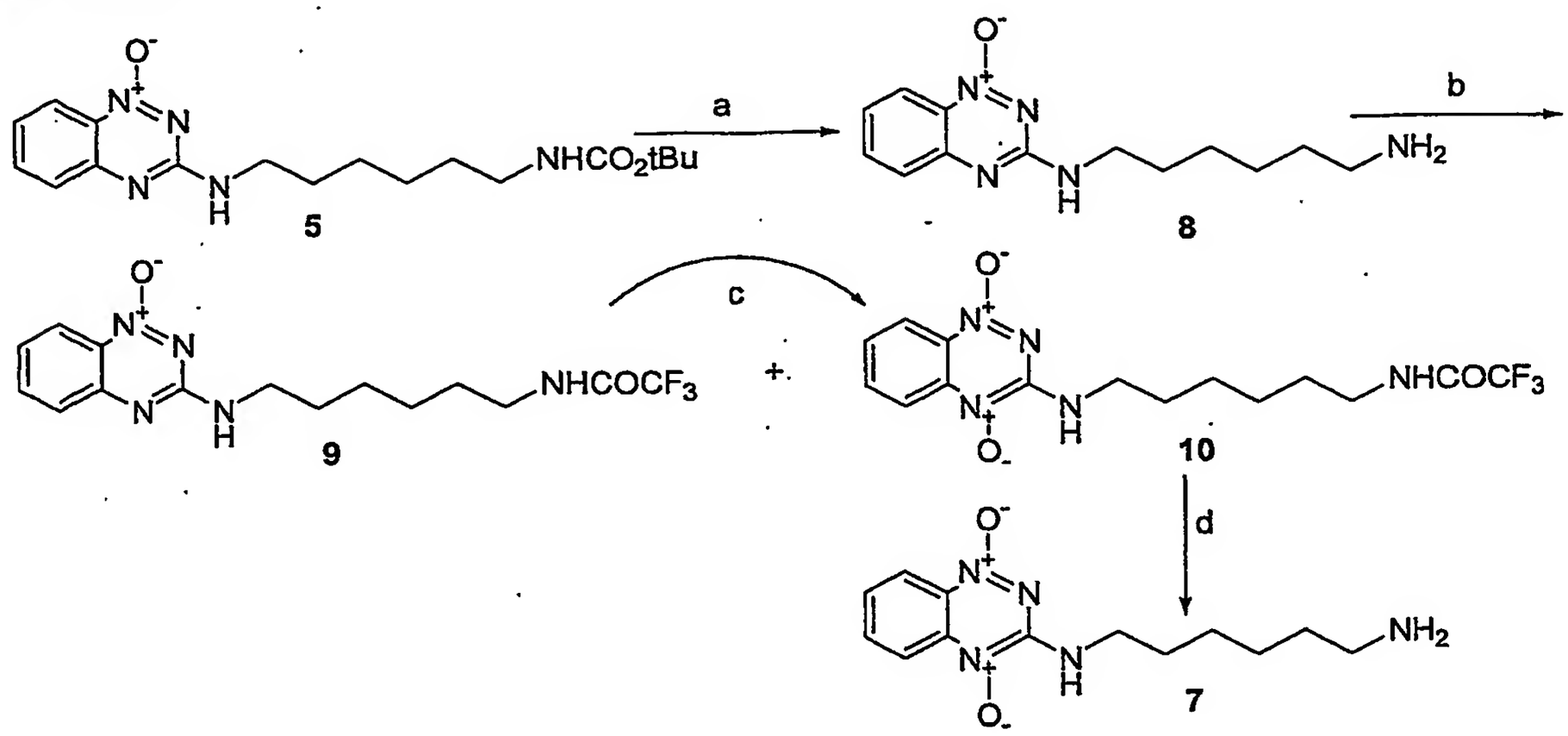
i) Et_3N, DCM, 65%;

j) MCPBA, DCM, 37% + 50% SM;

k) HCl, MeOH, 85%

An alternative approach to using trifluoroacetic anhydride to provide protection for the primary amine and to generate trifluoroperacetic acid *in situ* was also used (Scheme 4). Deprotection of carbamate **5** gave the amine **8**. Reaction of **8** with trifluoroacetic anhydride followed by 30% H_2O_2 gave a mixture of the 1-oxide **9** (22% yield) and 1,4-dioxide **10** (51% yield). 1-Oxide **9** was oxidised with trifluoroperacetic acid to give **10** (29% yield) as well as starting material **9** (61% yield). Deprotection of the trifluoroacetamide **10** provided 1,4-dioxide **7** in good yield.

Scheme 4



Reagents:

a) HCl, MeOH, 87%;

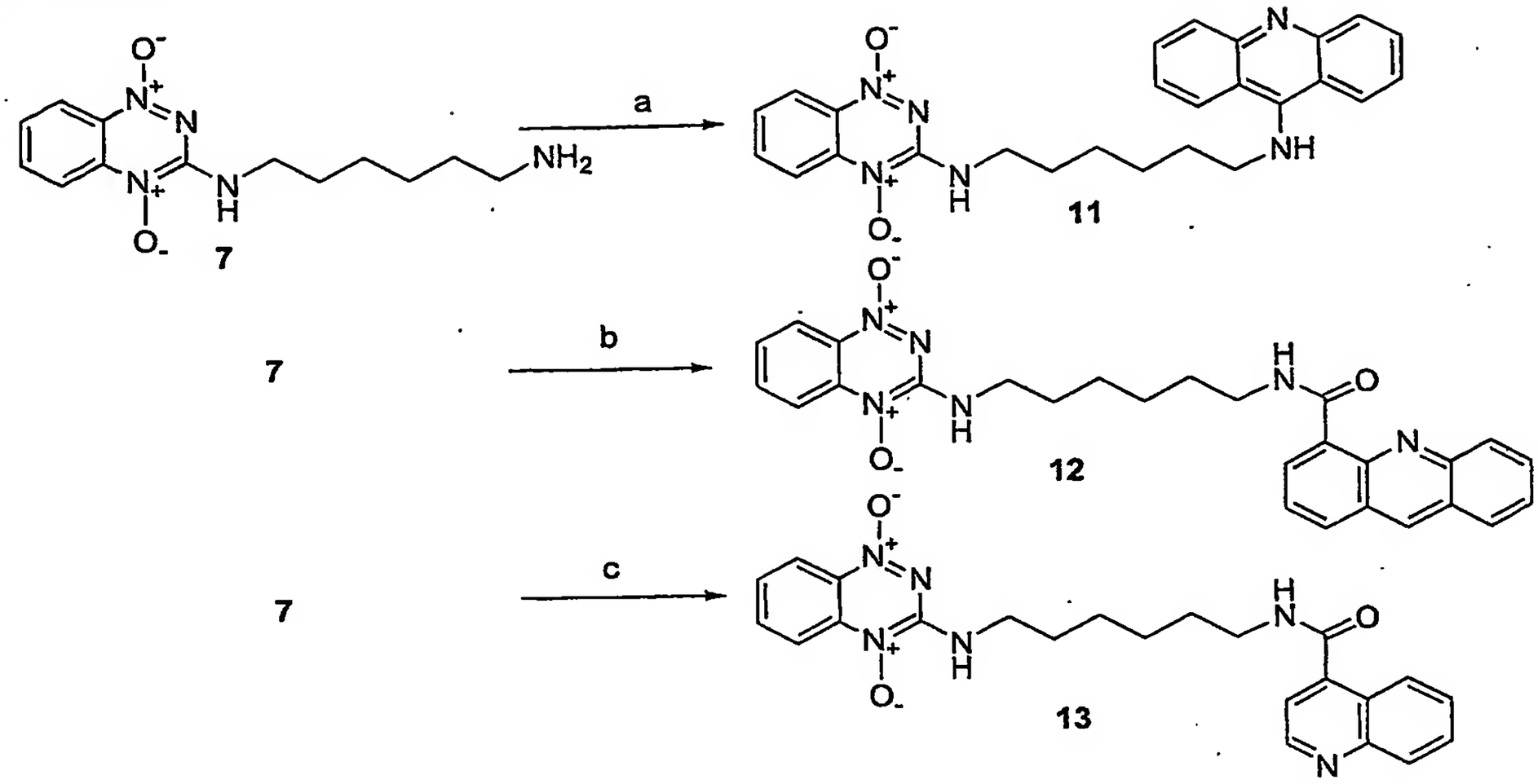
b) $(CF_3CO)_2O$, 35% H_2O_2, DCM, 51% + 10 (22%);

c) CF_3CO_3H, DCM, 29% + SM (61%);

d) NaOH, MeOH, 83%.

Coupling of 1,4 dioxide **7** with 9-methoxyacridine (Albert, "The Acridines" 2nd ed. 1966, Edward Arnold, London, p. 281) provided a compound of Formula I: the aminoacridine derivative **11** (Scheme 5). Similarly, reaction of **7** with 4-(1*H*-imidazol-1-ylcarbonyl)acridine (Spicer et al., *Anti-Cancer Drug Des.*, **1999**, 14, 281-289) gave **12**, a compound of Formula I. Similarly, reaction of the imidazolide of quinoline 4-acetic acid gave **13**, a compound of Formula I.

Scheme 5



Reagents:

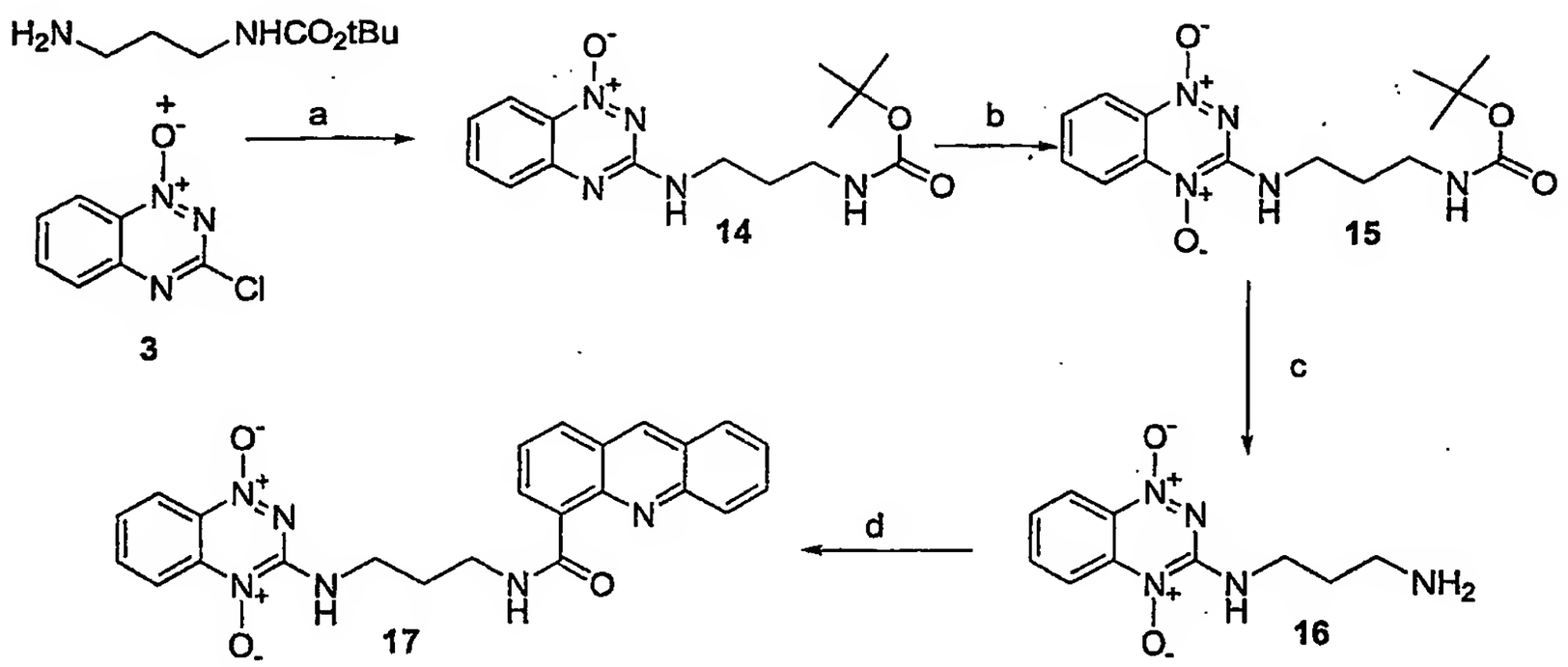
a) 9-methoxyacridine, MeOH, 60%;

b) acridine 4-carboxylic acid, CDI, DMF; **7**, THF, 91%;

c) quinoline 4-carboxylic acid, CDI, DMF, 80%; **7**, DMF/THF.

Reaction of chloride **3** with tert-butyl 3-aminopropylcarbamate gives **14**, which was oxidised to 1,4-dioxide **15** with MCPBA (Scheme 6). Deprotection of **15** under acid conditions gave amine **16** which was reacted with 4-(1*H*-imidazol-1-ylcarbonyl)acridine to give **17**, a compound of Formula I.

Scheme 6



Reagents:

a) Et_3N, DCM, 74%;

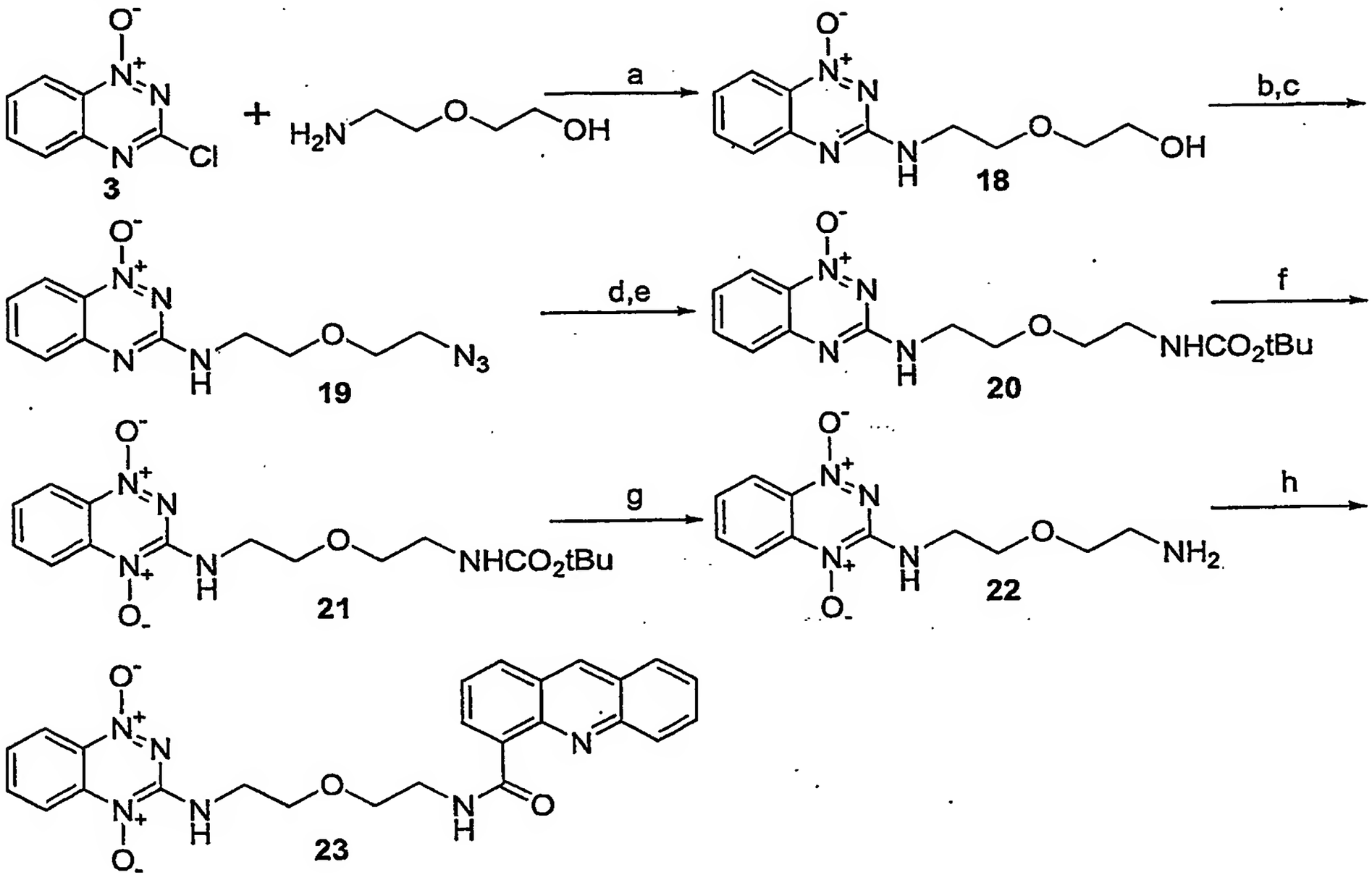
b) MCPBA, DCM, 24% + 45% SM ;

c) HCl, MeOH, 80%;

d) acridine 4-carboxylic acid, CDI, DMF; **16**, DCM, 80%.

Coupling of chloride **3** with 2-(aminoethoxy)ethanol gave alcohol **18** in 63% yield which was converted to the mesylate and displaced with sodium azide to give azide **19** in 89% yield (Scheme 7). Selective reduction of the azide group rather than 1-oxide of **19** could not be effected by hydrogenation using palladium on charcoal or Lindlar catalyst (Rolla et al., *J. Org. Chem.*, **1965**, 47, 4322-432). Other methods for reducing azides such as $NaBH_4$ under PTC (Corey et al., *Synth.*, **1975**, 590-591), BH_3.DMS (Hassner & Levy, *J. Amer. Chem. Soc.*, **1965**, 87, 4203-4204) or Staudinger conditions using $P(OEt)_3$ (Koziara & Zwierzak, *Synth.*, **1992**, 1063-1065) were ineffective. However, treatment of azide **19** with propane-1,3-dithiol and Et_3N in refluxing methanol (Bayley et al., *Tet. Lett.*, **1978**, 39, 3633-3634) provided the intermediate amine which was protected without isolation with di-*tert*-butyldicarbonate to give carbamate **20** in 93% yield for the two steps. Oxidation of **20** with MCPBA gave 1,4-dioxide **21** in 40% yield as well as recovered starting material (50%). Deprotection of **21** with trifluoroacetic acid gave amine **22** in 91% yield. Coupling of **22** with 4-(1*H*-imidazol-1-ylcarbonyl)acridine gave compound **23** in 97% yield.

Scheme 7



Reagents:

a) Et_3N, DCM, 63%;

b) MsCl, Et_3N, DCM;

c) NaN_3, DMF, 89% from 24;

d) propane-1,3-dithiol, Et_3N, MeOH;

e) BOC_2O, THF, 93% from 25;

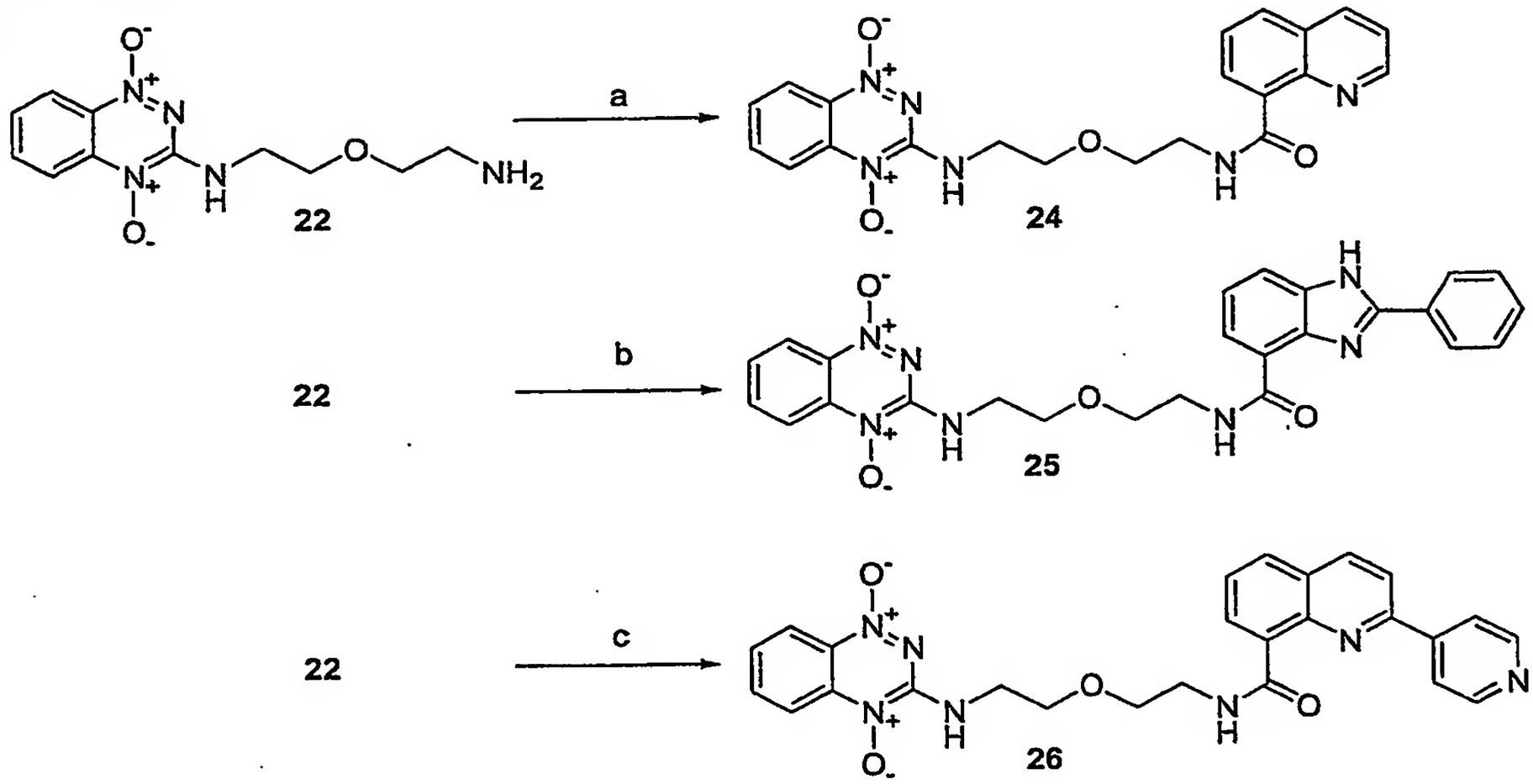
f) MCPBA, $NaHCO_3$, DCM, 40% + 50% SM;

g) CF_3CO_2H, DCM, 91%;

h) acridine 4-carboxylic acid, CDI, DMF; 28, THF, 97%.

Similarly, reaction of **22** with the imidazolides of 8-quinolinecarboxylic acid, 2-phenyl-1*H*-benzimidazole-4-carboxylic acid (Denny et al., *J. Med. Chem.* **1990**, 33, 814-819) and 2-(4-pyridinyl)-8-quinolinecarboxylic acid (Atwell et al., *J. Med. Chem.* **1989**, 32, 396-401) gave compounds of Formula I: **24**, **25**, and **26** respectively (Scheme 8).

Scheme 8



Reagents:

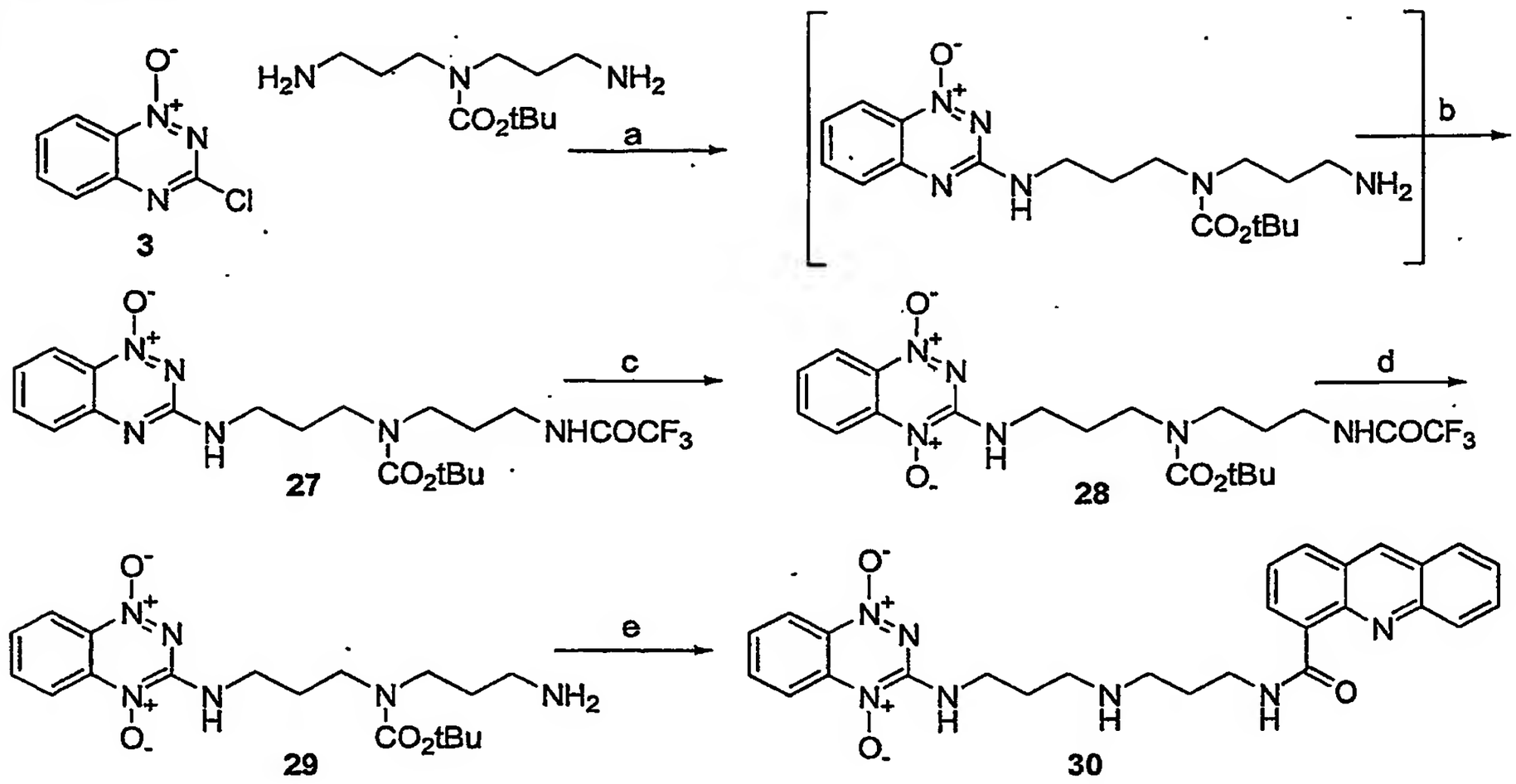
a) quinoline 8-carboxylic acid, CDI, DMF; **22**, DCM, 84%;

b) 2-phenylbenzimidaole 4-carboxylic acid, CDI, DMF; **22**, DCM, 86%;

c) 2-pyridylquinoline 8-carboxylic acid, CDI, DMF; **22**, DCM, 70%.

Reaction of chloride **3** with *tert*-butyl bis(3-aminopropyl)carbamate and protection of the intermediate primary amine with trifluoroacetic anhydride gave the trifluoroacetamide **27** in 39% for the two steps (Scheme 9). Oxidation of **27** with MCPBA gave the 1,4-dioxide **28** (8% with 65% recovered starting material). Deprotection of **28** gave amine **29** in good yield which was coupled to 4-(1*H*-imidazol-1-ylcarbonyl)acridine to give compound **30**, a compound of Formula I.

Scheme 9



Reagents:

a) Et_3N, DCM;

b) $(CF_3CO)_2O$, DCM, 22% from **3**;

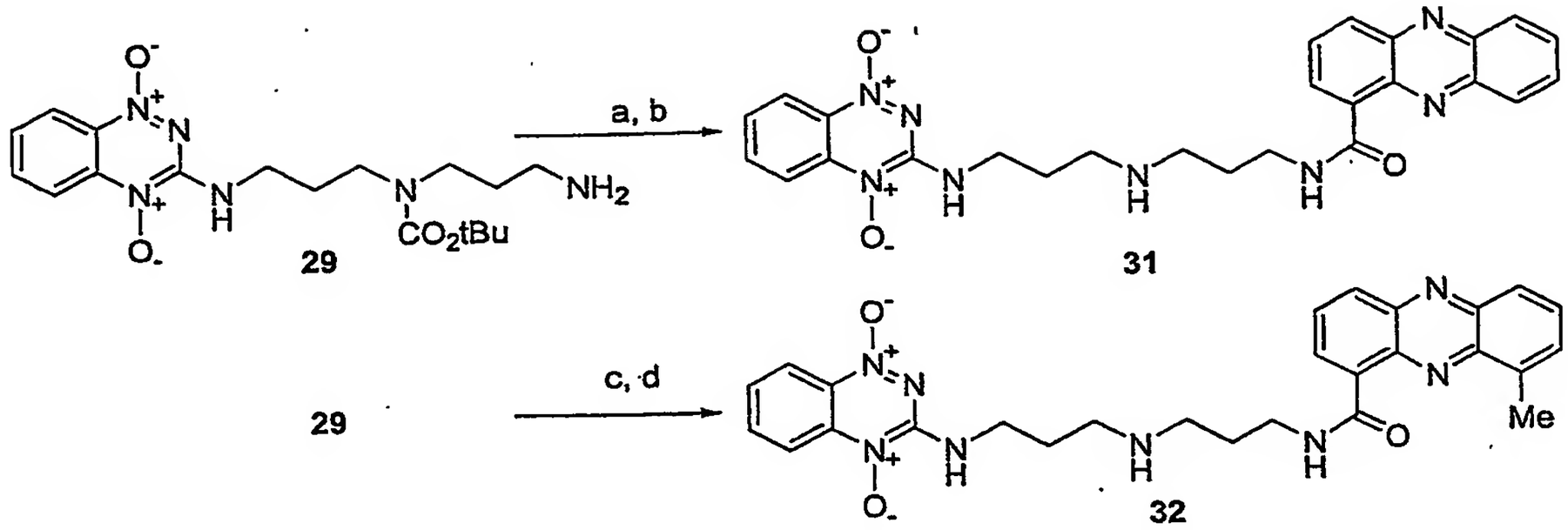
c) MCPBA, $NaHCO_3$, DCM, 8% + 65% SM;

d) K_2CO_3, MeOH, H_2O, 74%;

e) acridine 4-carboxylic acid, CDI, DMF; **30**, DCM, 67%; HCl, MeOH, 90%.

Similarly, reaction of amine **29** with imidazolides of phenazine and 9-methylphenazine followed by deprotection under acidic conditions gave compounds **31** and **32**, respectively (Scheme 10).

Scheme 10



Reagents:

a) phenazine 1-carboxylic acid, CDI, DMF; **29**, DCM, 40%.

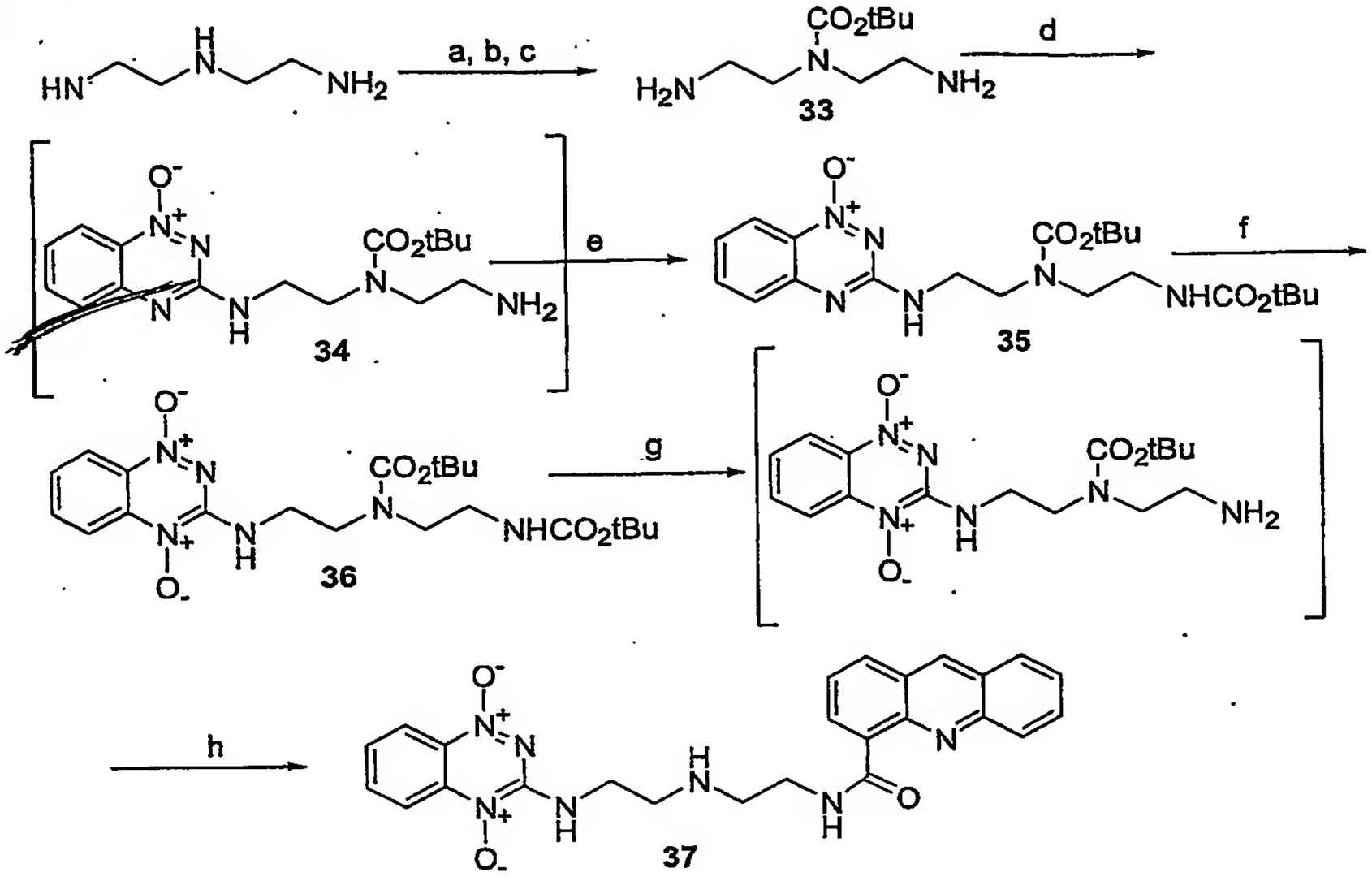
b) HCl, MeOH, 85%.

c) 9-methylphenazine 1-carboxylic acid, CDI, DMF; **29**, DCM, 40%.

d) HCl, MeOH, 86%.

Reaction of chloride **3** with amine **33**, prepared from N^1-(2-aminoethyl)-1,2-ethanediamine gave the 1-oxide **34** (Scheme 11). Compound **34** was protected as carbamate **35** and oxidized with MCPBA to give dioxide **36**. Deprotection and coupling of the intermediate amine with the imidazolide of acridine 4-carboxylic acid gave compound **37**, a compound of Formula I.

Scheme 11



Reagents:

a) CF_3CO_2Et, ether, 61%;

b) $(BOC)_2O$, quant;

c) aq. NH_3, MeOH, quant;

d) **3**, Et_3N, DME, 72%;

e) $(BOC)_2O$, DCM, 52%;

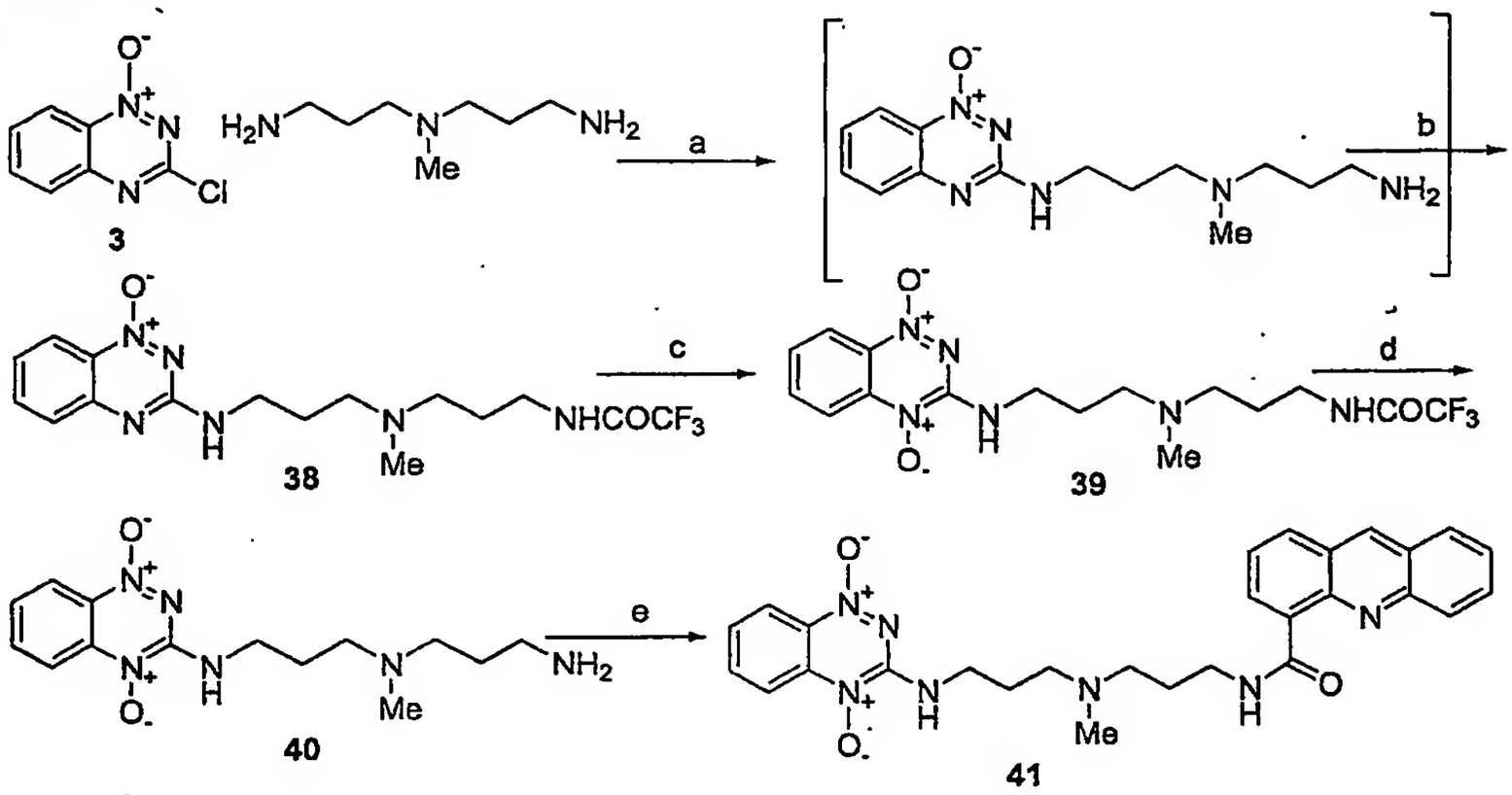
f) MCPBA, DCM, 39% + 62% SM;

g) HCl, MeOH, 76%;

h) acridine-4-carboxylic acid, CDI, DMF, 99%.

Reaction of chloride **3** with N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine and protection of the intermediate amine gave acetamide **38** in 43% yield (Scheme 12). Oxidation of **38** with trifluoroperacetic acid under acidic conditions resulted in selective aromatic N-oxidation to give 1,4-dioxide **39** (27%) and recovered starting material **38** (24%). Deprotection of **39** gave amine **40** which was coupled with 4-(1*H*-imidazol-1-ylcarbonyl)acridine to give compound **41**, a compound of Formula I, in 66% yield.

Scheme 12



Reagents:

a) Et_3N, DCM;

b) $(CF_3CO)_2O$, DCM, 43% from **3**;

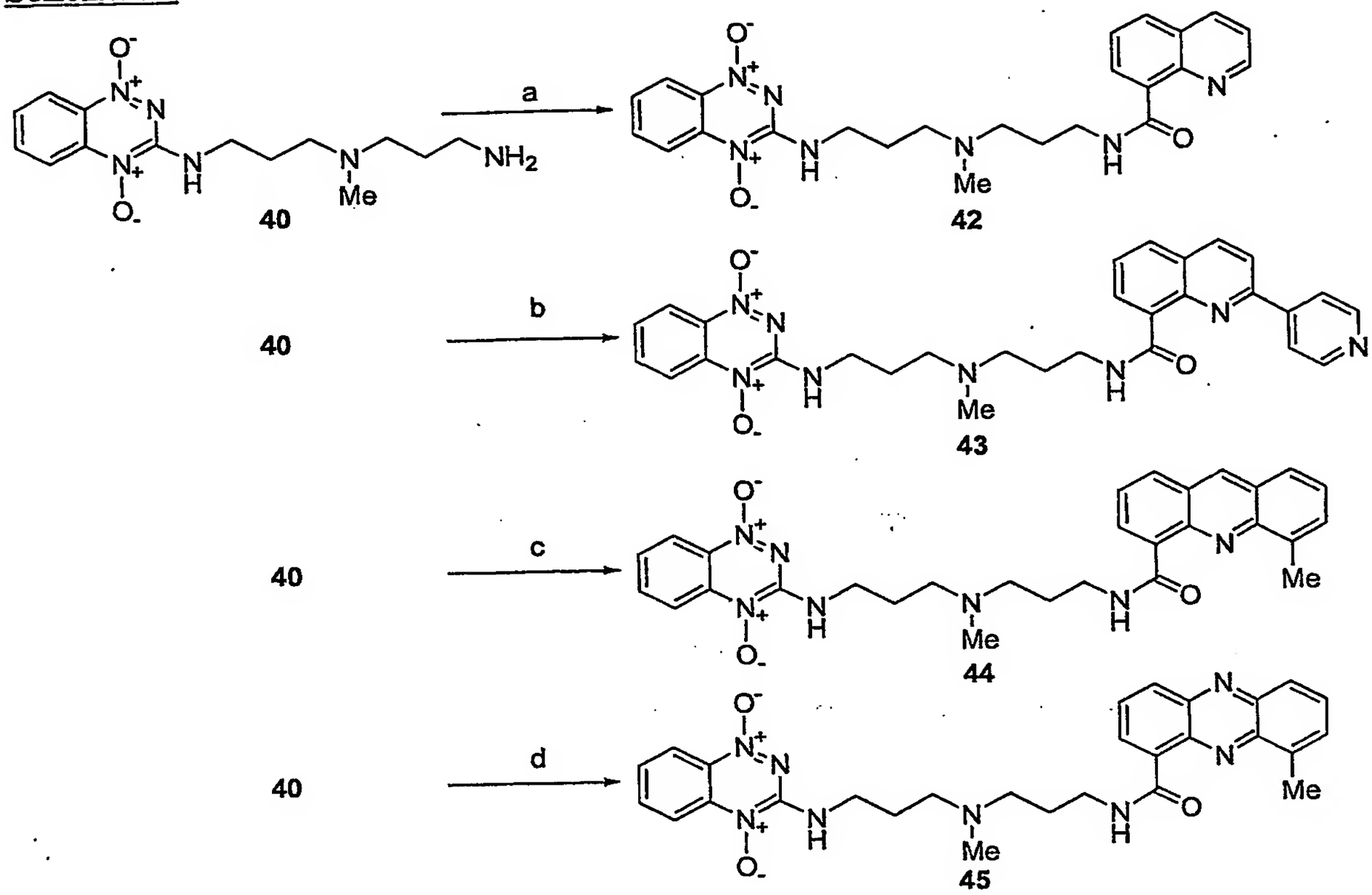
c) MCPBA, $NaHCO_3$, DCM, 27% + 24% SM;

d) NH_4OH, MeOH, quant.;

e) acridine 4-carboxylic acid, CDI, DMF; **40**, DCM, 66%.

Similarly, reaction of **40** with the imidazolides of 8-quinolinecarboxylic acid, 2-(4-pyridinyl)-8-quinolinecarboxylic acid (Atwell et al., *J. Med. Chem.* **1989**, 32, 396-401), 5-methyl-4-acridine carboxylic acid, and 9-methyl-4-phenazinecarboxylic acid gave compounds **42**, **43**, **44**, and **45** respectively (Scheme 13).

Scheme 13



Reagents:

a) quinoline 8-carboxylic acid, CDI, DMF; **40**, DCM, 91%;

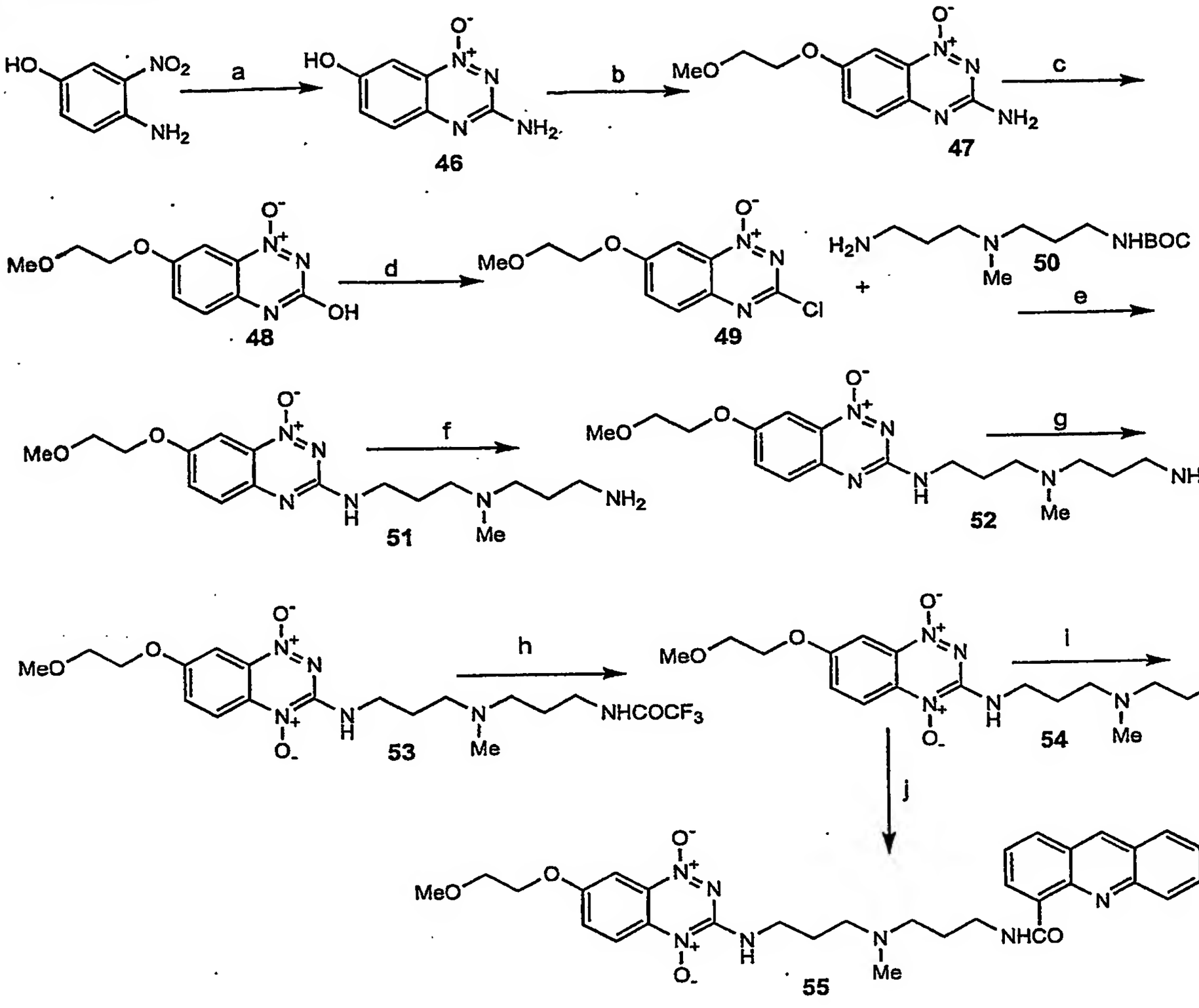
b) 2-pyridylquinoline 8-carboxylic acid, CDI, DMF; **40**, DCM, 94%;

c) 5-methylacridine-4-carboxylic acid, CDI, DMF; **40**, DCM, 88%;

d) 9-methylphenazine-4-carboxylic acid, CDI, DMF; **40**, DCM, 90%.

Reaction of 4-amino-3-nitrophenol with cyanamide under acidic conditions followed by condensation under basic conditions gave the phenol **46** (Friebe et. al. US Patent 5,856,325, Jan 5, 1999), which was alkylated under basic conditions to give ether **47** (Scheme 14). Diazotization of **47** gave **48**, which was chlorinated with $POCl_3$ to give chloride **49**. Coupling of chloride **49** with amine **50** gave the 1-oxide **51**. Protection of **51** as the trifluoroacetamide **52** and oxidation with trifluoroperacetic acid gave the dioxide **53**. Deprotection of **53** gave intermediate amine **54**, which was coupled with the imidazolide of acridine-4-carboxylic acid to give compound **55**, a compound of Formula I.

Scheme 14



Reagents:

a) NH_2CN, HCl; NaOH, 97%;

b) $MeOCH_2CH_2Br$, K_2CO_3, DMF, 77%;

c) $NaNO_2$, HCl, 68%;

d) $POCl_3$, 83%;

e) Et_3N, DME, 98%;

f) CF_3CO_2Et, H_2O, MeCN, 87%;

g) CF_3CO_3H, DCM, 30%;

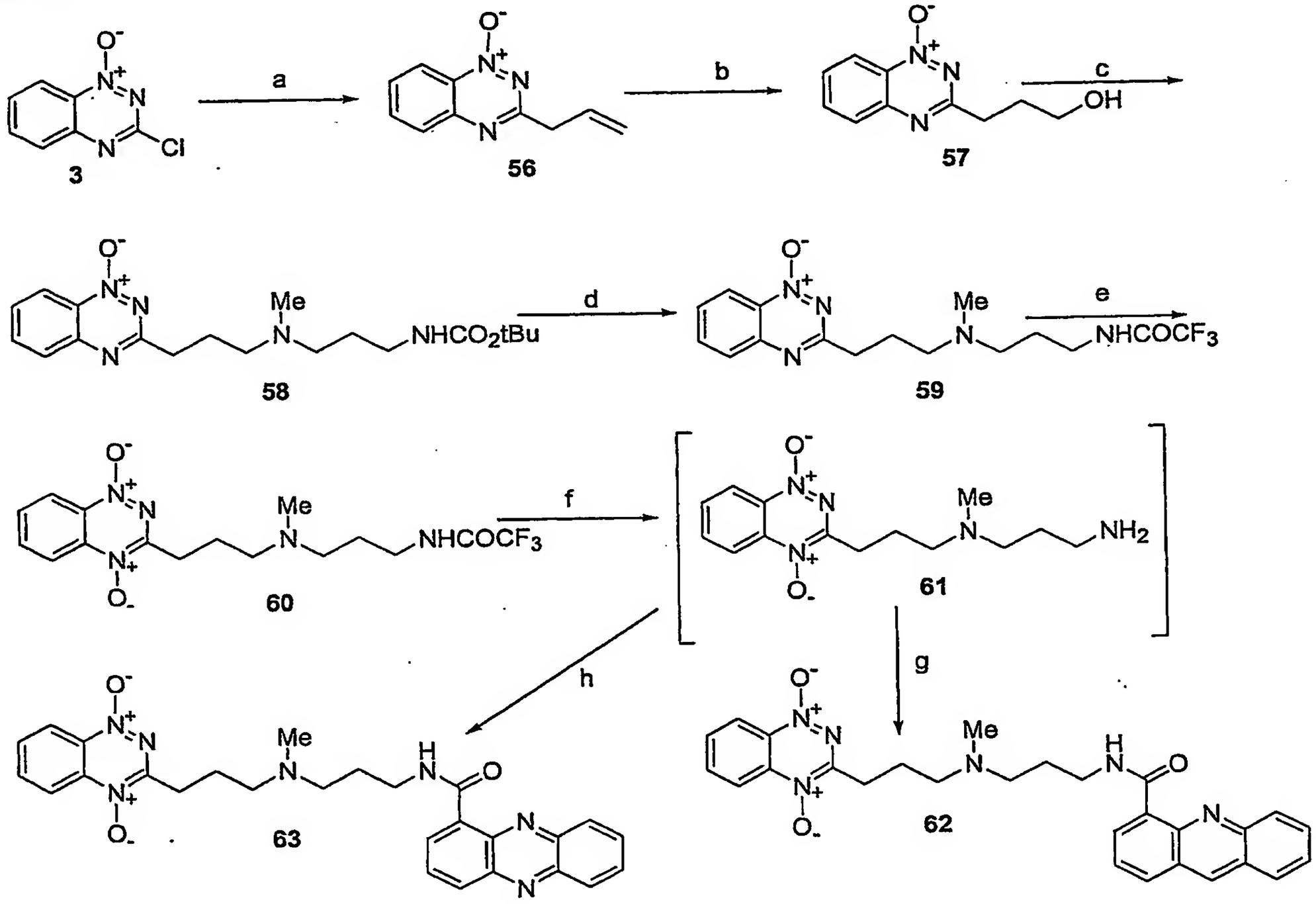
h) aq. NH_3, MeOH;

i) acridine-4-carboxylic acid, CDI, DMF; 54, THF, 79% (two steps).

Reaction of chloride **3** with allyltributyltin in the presence of tetrakis-palladiumtriphenylphosphine in DME at reflux temperature gave alkene **56** in high yield (Scheme 15). Hydroboration of **56** gave the alcohol **57** which was activated with

methanesulfonyl chloride and reacted with *tert*-butyl 3-aminopropylcarbamate to give the amine **58**. Conversion to the trifluoroacetamide **59** and oxidation with trifluoroperacetic acid gave the 1,4-dioxide **60**, which was deprotected under basic conditions to give amine **61**. Coupling of amine **61** with the imidazolide of acridine-4-carboxylic acid gave compound **62**, a compound of Formula I. Similarly, coupling of amine **61** with the imidazolide of phenazine-4-carboxylic acid gave compound **63**, a compound of Formula I.

Scheme 15



Reagents:

a) allylSnBu$_3$, Pd(PPh$_3$)$_4$, DME, 93%;

b) 9-BBN, THF; 30% H_2O_2, 3 M NaOH, 87%;

c) MsCl, Et_3N, DCM; *tert*-butyl 3-aminopropylcarbamate, DMF, 48%;

d) HCl, MeOH; CF_3CO_2Et, H_2O, MeCN, 92%;

e) CF_3CO_3H, CF_3CO_2H, $CHCl_3$, 57%;

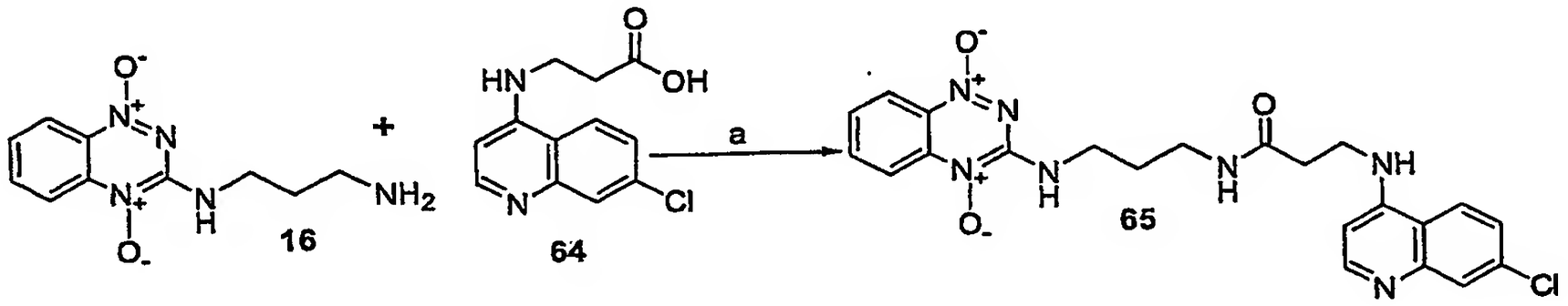
f) aq. NH_3, MeOH;

g) acridine-4-carboxylic acid, CDI, DMF; **61**, THF, 40% (two steps);

h) phenazine-1-carboxylic acid, CDI, DMF; **61**, THF, 56% (two steps).

Reaction of amine **16** with the imidazolide of *N*-(7-chloro-4-quinolinyl)-β-alanine (**64**) (Titus et al, *J. Org. Chem.*, **1948**, *13*, 39-62) gave amide **65**, a compound of Formula I (Scheme 16).

Scheme 16

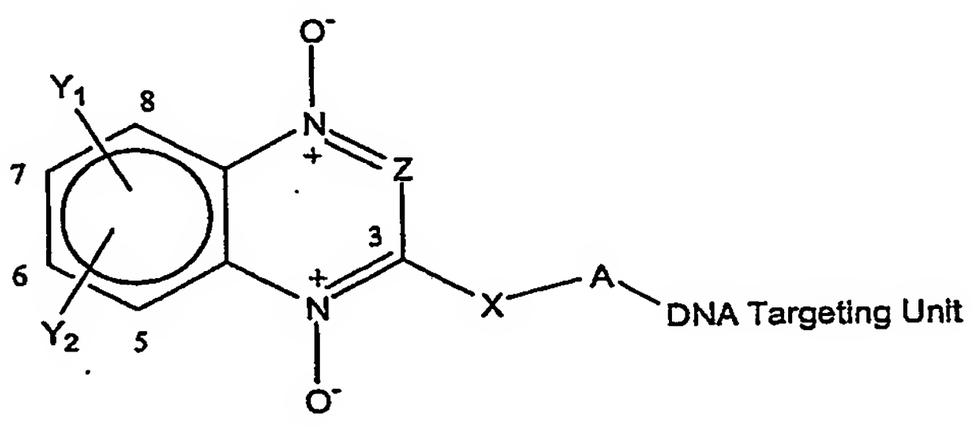


Reagents:

a) *N*-(7-chloro-4-quinolinyl)-β-alanine, CDI, DMF; **16**, DMF, 46%.

Examples of the compounds of the invention

Table 1 gives details on examples of compounds within the scope of the invention, and preparable by the methods of the invention.



I

Table 1

No.	#	Y	Z	X	A	DNA targeting unit	mp (°C)	Anal
11	3	H	N	NH	$(CH_2)_6$	9-NHacridine	118-119	C,H,N
12	3	H	N	NH	$(CH_2)_6$	4-NHCOacridine	196-198	C,H,N
13	3	H	N	NH	$(CH_2)_6$	4-NHquinoline	196-198	C,H,N
17	3	H	N	NH	$(CH_2)_3$	4-NHCOacridine	192	C,H,N
23	3	H	N	NH	$(CH_2)_2O(CH_2)_2$	4-NHCOacridine	98-100	C,H,N
24	3	H	N	NH	$(CH_2)_2O(CH_2)_2$	8-NHCOquinoline	168-170	C,H,N
25	3	H	N	NH	$(CH_2)_2O(CH_2)_2$	4-NHCObenz-imidazole-2-phenyl	203-207	C,H,N
26	3	H	N	NH	$(CH_2)_2O(CH_2)_2$	8-NHCOquinoline-2-(4-pyridyl)	128-130	C,H,N
30	3	H	N	NH	$(CH_2)_3NH(CH_2)_3$	4-NHCOacridine	gum	C,H,N
31	3	H	N	NH	$(CH_2)_3NH(CH_2)_3$	1-NHCOphenazine	163-169	C,H,N
32	3	H	N	NH	$(CH_2)_3NH(CH_2)_3$	1-NHCO-9-methyl-phenazine	183-186	HRMS
37	3	H	N	NH	$(CH_2)_2NH(CH_2)_2$	4-NHCOacridine	151-154	C,H,N
41	3	H	N	NH	$(CH_2)_3NMe(CH_2)_3$	4-NHCOacridine	169-171	HRMS
42	3	H	N	NH	$(CH_2)_3NMe(CH_2)_3$	8-NHCOquinoline	119-121	C,H,N
43	3	H	N	NH	$(CH_2)_3NMe(CH_2)_3$	8-NHCO-2-(4-pyridyl)quinoline	179-181	C,H,N
44	3	H	N	NH	$(CH_2)_3NMe(CH_2)_3$	4-NHCO-5-methylacridine	158-162	C,H,N
45	3	H	N	NH	$(CH_2)_3NMe(CH_2)_3$	1-NHCO-9-methylphenazine	138-142	C,H,N
55	3	†	N	NH	$(CH_2)_3NMe(CH_2)_3$	4-NHCOacridine	98-103	HRMS
62	3	H	N	CH_2	$(CH_2)_2NMe(CH_2)_3$	4-NHCOacridine	gum	HRMS
63	3	H	N	CH_2	$(CH_2)_2NMe(CH_2)_3$	1-NHCOphenazine	173	HRMS
65	3	H	N	NH	$(CH_2)_3NHCO(CH_2)_2$	4-NH-7-Clquinoline	202	HRMS

Side chain position

†7-$MeOCH_2CH_2O$-

In the following examples representative of the invention and the detailed methods for preparing them:

Elemental analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ.

Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. IR spectra were recorded on a Midac FT-IR as KBr discs, unless otherwise stated.

NMR spectra were obtained on a Bruker AM-400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C spectra. Spectra were obtained in $CDCl_3$ unless otherwise specified, and are referenced to Me_4Si. Chemical shifts and coupling constants were recorded in

units of ppm and Hz, respectively. Assignments were determined using COSY, HSQC, and HMBC two-dimensional experiments.

Mass spectra were determined on a VG-70SE mass spectrometer using an ionizing potential of 70 eV at a nominal resolution of 1000. High-resolution spectra were obtained at nominal resolutions of 3000, 5000, or 10000 as appropriate. All spectra were obtained as electron impact (EI) using PFK as the reference unless otherwise stated. Solutions in organic solvents were dried with anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure on a rotary evaporator.

Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F_{254}) with visualization of components by UV light (254 nm) or exposure to I_2.

Column chromatography was carried out on silica gel, (Merck 230-400 mesh). All compounds designated for biological testing were analysed at >99% purity by reverse phase HPLC using a Philips PU4100 liquid chromatograph, a Phenomenex BondClone 10-C18 stainless steel column (300mm x 3.9 mm i.d.) and a Philips PU4120 diode array detector. Chromatograms were run using various gradients of aqueous (1 M NaH_2PO_4, 0.75 M heptanesulfonic acid, 0.5 M dibutylammonium phosphate, and MilliQ water in a 1:1:1:97 ratio) and organic (80% MeOH/MilliQ water) phases. DCM refers to dichloromethane; DME refers to dimethoxyethane, DMF refers to dry dimethyl formamide; ether refers to diethyl ether; EtOAc refers to ethyl acetate; EtOH refers to ethanol; MeOH refers to methanol; pet. ether refers to petroleum ether, boiling range 40-60 °C; THF refers to tetrahydrofuran dried over sodium benzophenone ketyl. All solvents were freshly distilled.

Example A.

3-[(6-Aminohexyl)amino]-1,2,4-benzotriazine 1,4-dioxide (7).

3-Chloro-1,2,4-benzotriazine 1-oxide (3). 2-Nitroaniline (10 g, 72.4 mmol) and cyanamide (14.0 g, 330 mmol) were melted together and cHCl (20 mL) added cautiously. The mixture was heated at 100 °C until the foaming subsided. The mixture was made strongly alkaline with 30% w/v NaOH and heated at 100 °C for 10 min. The suspension was cooled to 25 °C and the yellow solid filtered, washed with water (20 mL) and dried. A small sample was recrystallized to give 3-amino-1,2,4-benzotriazine 1-oxide (1) mp (MeOH/EtOAc) 267-269 °C; lit. [Arndt, *Ber.* **1913**, 46, 3522-3529] mp (EtOH) 269 °C]. The remainder was dissolved in 2 M HCl (300 mL),

cooled to 5 °C, and a solution of $NaNO_2$ (10 g, 0.145 mol) in water (100 mL) added dropwise. The resulting precipitate was filtered, dissolved in dilute NH_3, filtered, and acidified with cHCl. The precipitate was filtered, washed with water and dried to give 3-hydroxy-1,2,4-benzotriazine 1-oxide (**2**) (5.77 g, 49%) as a yellow powder, mp 209-212 °C; lit. [Arndt, *Ber.* **1913**, 46, 3522-3529] mp (H_2O) 219 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 8.14 (d, J = 8.4 Hz, 1 H, H 8), 7.77-7.81 (m, 1 H, H 6), 7.54 (d, J = 8.4 Hz, 1 H, H 5), 7.90 (m, 3 H, H 7, NH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2, 148.7, 135.6, 129.8, 125.8, 124.6, 119.8. A mixture of the alcohol (**2**) (5.7 g, 34.9 mmol), *N,N*-dimethylaniline (11 mL, 87.3 mmol), and $POCl_3$ (23 mL, 244 mmol) was heated at reflux temperature for 1 h then poured on to ice. The resulting solid was filtered and recrystallized to give 3-chloro-1,2,4-benzotriazine 1-oxide (**3**) (3.77 g, 59%) as a pale yellow powder, mp 119-119.5 °C; lit. [Robbins *et al.*, *J. Chem. Soc.*, **1957**, 3186-3194] (MeOH) 117-118 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 8.38 (dd, J = 8.7, 1.0 Hz, 1 H, H 8), 8.16 (ddd, J = 8.3, 7.0, 1.3 Hz, 1 H, H6), 8.06 (dd, J = 8.2, 1.0 Hz, 1 H, H 5), 7.90 (ddd, J = 8.7, 6.9, 1.3 Hz, 1 H, H 7); ^{13}C NMR [$(CD_3)_2SO$] δ 155.3, 146.9, 137.2, 133.9, 131.5, 128.0, 119.9.

6-*t*-Butyloxycarbamoylhexylamine (4). A solution of di-*t*-butyldicarbonate (18.6 g, 85.3 mmol) in dry DCM (100 mL) was added dropwise to a stirred solution of 6-aminohexanol (10.0 g, 85.3 mmol) in dry DCM (100 mL) at 20 °C and stirred for 16 h. The solution was washed with dilute aqueous Na_2CO_3 solution (100 mL), 0.1 M HCl (100 mL), water (100 mL), brine (50 mL), dried and the solvent evaporated. The residue was dissolved in DCM (250 mL) and Et_3N (15.5 mL, 111 mmol) added. A solution of methanesulfonyl chloride (7.3 mL, 94 mmol) was added dropwise and the mixture stirred at 20 °C for 16 h. The solution was washed with saturated aqueous $KHCO_3$ (100 mL), water (2 × 100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was dissolved in DMF (100 mL) and NaN_3 (5.55 g, 85.3 mmol) added. The mixture was stirred at 100 °C for 1 h, the solvent evaporated and the residue partitioned between EtOAc (200 mL) and water (200 mL). The organic fraction was washed with water (200 mL), brine (100 mL), dried and the solvent evaporated. The residue was chromatographed, eluting with 30% EtOAc/pet. ether, to give the 6-*t*-butyloxycarbamoylhexyl azide (17.5 g, 85%) as a colorless oil, ^{1}H NMR δ 4.53 (br s, 1 H, OCONH), 3.52 (t, J = 6.9 Hz, 2 H, CH_2N), 3.11 (dt, J = 6.5, 6.4 Hz,

2 H, CH_2N), 1.57-1.63 (m, 2 H, CH_2), 1.44-1.52 (m, 11 H, CH_2, $C(CH_3)_3$), 1.30-1.40 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 156.0, 79.1, 51.3, 40.4, 29.9, 28.7, 28.4 (3), 26.4, 26.3. A mixture of azide (14.81 g, 61.1 mol) and Pd/C (0.5 g) in EtOAc/EtOH (200 mL) was stirred at 20 °C under hydrogen (60 psi) for 1 h. The mixture was filtered through celite, the cake washed with EtOAc (3 × 30 mL) and the solvent evaporated to give **4** (12.82 g, 97%) as a white solid, mp (EtOAc) 89-91 °C; ^1H NMR δ 4.65 (br s, 1 H, OCONH), 3.52 (br s, 2 H, NH_2), 2.69 (t, J = 6.9 Hz, 2 H, CH_2N), 1.88 (br s, 2 H, CH_2N), 1.44-1.50 [m, 13 H, 2 × CH_2, $C(CH_3)_3$], 1.29-1.35 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 156.0, 78.9, 41.9, 40.4, 33.4, 29.9, 28.3 (3), 26.5, 26.4.

3-[(6-*t*-Butyloxycarbamoylhexyl)amino]-1,2,4-benzotriazine 1-oxide (5). A solution of amine **4** (12.8 g, 61.1 mmol) in DCM was added to a stirred solution of chloride **3** (3.70 g, 20.4 mmol) and Et_3N (5.7 mL, 40.8 mmol) in DCM (100 mL) and the solution stirred at 20 °C for 96 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (30-100%) of EtOAc/pet. ether, to give 1-oxide **5** (4.77 g, 65%) as a yellow powder, mp (EtOAc/pet. ether) 154-156 °C; ^1H NMR δ 8.26 (d, J = 8.6 Hz, 1 H, H 8), 7.70 (dd, J = 8.2, 7.2 Hz, 1 H, H 6), 7.59 (d, J = 8.5 Hz, 1 H, H 5), 7.27 (dd, J = 8.0, 7.5 Hz, 1 H, H 7), 5.34 (br s, 1 H, NH), 4.55 (br s, 1 H, OCONH), 3.51 (dd, J = 6.8, 6.6 Hz, 2 H, CH_2N), 3.10-3.13 (m, 2 H, CH_2N), 1.64-1.72 (m, 2 H, CH_2), 1.48-1.54 (m, 2 H, CH_2), 1.44 [s, 9 H, $C(CH_3)_3$], 1.38-1.43 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 158.9, 155.5, 148.9, 135.5, 130.8, 126.4, 124.8, 120.4, 79.0, 41.2, 40.3, 30.0, 29.2, 28.4 (3), 26.4, 26.3; Anal. calc. for $C_{18}H_{27}N_5O_3$: C, 59.8; H, 7.5; N, 19.4; found: C, 59.6; H, 7.7; N, 19.2%.

3-[(6-*t*-Butyloxycarbamoylhexyl)amino]-1,2,4-benzotriazine 1,4-dioxide (6). A solution of MCPBA (1.48 g, 6.02 mmol) in DCM (20 mL) was added dropwise to a stirred solution of 1-oxide **5** (1.45 g, 4.01 mmol) in DCM (100 mL) at 20 °C and the solution stirred for 4 h. The solution was partitioned between DCM (200 mL) and saturated $KHCO_3$ solution (200 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed on neutral alumina, eluting with 50% EtOAc/DCM then a gradient (0-10%) MeOH/$CHCl_3$, to give (i) starting material **5** (0.73 g, 50%), and (ii) 1,4-dioxide **6** (0.55 g, 37%) as a yellow powder, mp (EtOAc/DCM) 132-134 °C; IR (KBr) υ 3367, 3260, 1688, 1622, 1362, 1173 cm^{-1};

NMR [$(CD_3)_2SO$] δ 8.30 (dd, J = 6.3, 6.1 Hz, 1 H, OCONH), 8.19 (d, J = 8.5 Hz, 1 H, H 8), 8.12 (d, J = 8.5 Hz, 1 H, H 5), 7.91-7.95 (m, 1 H, H 6), 7.53-7.57 (m, 1 H, H 7), 6.76 (br s, 1 H, NH), 3.32-3.39 (m, 2 H, CH_2N), 2.87-2.92 (m, 2 H, CH_2N), 1.56-1.61 (m, 2 H, CH_2), 1.32-1.40 [m, 13 H, 2 × CH_2, $C(CH_3)_3$], 1.25-1.31 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 155.5, 149.7, 138.1, 135.4, 129.8, 126.8, 121.1, 116.8, 77.2, 40.6, 39.8, 29.4, 28.6, 28.2 (3), 25.9, 25.8; Anal. calc. for $C_{18}H_{27}N_5O_4 \cdot ¼H_2O$: C, 56.6; H, 7.3; N, 18.3; found: C, 56.8; H, 7.3; N, 16.8%.

***N*^{1}-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (7).** HCl gas was bubbled through a solution of carbamate **6** (204 mg, 0.54 mmol) in MeOH (20 mL) for 2 minutes and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between $CHCl_3$ (100 mL) and saturated $KHCO_3$ solution (100 mL). The aqueous fraction was further extracted with $CHCl_3$ (3 × 30 mL), the combined organic extracts dried, and the solvent evaporated to give amine **7** (127 mg, 85%) as a red powder, mp 120-122 °C, IR (KBR) υ 3250, 2926, 1616, 1599, 1410, 1356, 1078 cm^{-1}; ^1H NMR δ 8.34 (d, J = 8.5 Hz, 1 H, H 8'), 8.29 (d, J = 8.6 Hz, 1 H, H 5'), 7.87-7.90 (m, 1 H, H 6'), 7.48-7.52 (m, 1 H, H 7'), 7.13 (s, 1 H, NH), 3.60 (t, J = 7.1 Hz, 2 H, CH_2N), 2.70 (t, J = 6.8 Hz, 2 H, CH_2N), 1.70-1.76 (m, 2 H, CH_2), 1.35-1.50 (m, 6 H, 3 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 149.7, 138.1, 135.4, 129.8, 126.7, 121.0, 116.8, 41.5, 40.6, 33.1, 28.7, 26.1, 26.0; Anal. calc. for $C_{13}H_{19}N_5O_2$: C, 56.3; H, 6.9; N, 25.3; found: C, 56.3; H, 6.8; N, 22.2%. The compound was dissolved in MeOH, treated with HCl gas, and the solvent evaporated. The residue was crystallized to give the dihydrochloride of **7** as a red powder, mp (MeOH/EtOAc) 150 °C (dec.).

***N*^{1}-(1-Oxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (8).** HCl gas was bubbled through a solution of carbamate **5** (1.0 g, 2.77 mmol) in MeOH (80 mL) for 2 minutes and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between $CHCl_3$ (100 mL) and Na_2CO_3 solution (100 mL). The aqueous fraction was further extracted with $CHCl_3$ (3 × 30 mL), the combined organic extracts dried, and the solvent evaporated to give amine **8** (0.63 g, 87%) as a red powder, mp 132-134 °C, ^1H NMR δ 8.25 (dd, J = 8.6, 1.0 Hz, 1 H, H 8'), 7.66-7.71 (m, 1 H, H 6'), 7.59 (d, J = 8.4 Hz, 1 H, H 5'), 7.26-7.30 (m, 1 H, H 7'), 5.48 (br s, 1 H, NH), 3.52 (dd, J = 6.9, 6.3 Hz, 2 H, H 1), 2.69 (dd, J = 6.8, 6.6 Hz, 2 H, H 6), 1.64-1.71 (m, 2 H,

H 2), 1.35-1.48 (m, 8 H, H 3, H 4, H 5, NH_2); ^{13}C NMR δ 159.0, 148.9, 135.5, 130.8, 126.4, 124.7, 120.4, 42.0, 41.3, 33.6, 29.3, 26.6, 26.5; Anal. calc. for $C_{13}H_{19}N_5O$: C, 59.7; H, 7.3; N, 26.8; found: C, 59.5; H, 7.5; N, 26.5%.

Oxidation of N^1-(1-oxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (8). Trifluoroacetic anhydride (11.9 mL) was added to a stirred solution of amine **8** (1.1 g, 4.2 mmol) in DCM (100 mL) and the solution stirred at 20 C for 30 min. The solution was cooled to 5 °C and 35% H_2O_2 (11.9 mL, ca 105 mmol) added dropwise and the mixture stirred vigorously for 16 h. The mixture was concentrated to 30 mL (CAUTION) and partitioned between DCM (100 mL) and sat. aq. $KHCO_3$ solution (50 mL). The aqueous fraction was extracted with DCM (3 × 50 mL), the combined organic fraction dried and the solvent evaporated (CAUTION). The residue was chromatographed, eluting with a gradient (0-10%) MeOH/(40-0%) EtOAc/DCM, to give (i) 2,2,2-trifluoro-*N*-{6-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]hexyl}acetamide (**9**) (0.77 g, 51%) as a yellow solid, mp (EtOAc/DCM) 188-189 °C; IR (KBr) υ 3306, 1699, 1588, 1570, 1176 cm^{-1}; ^1H NMR δ 8.27 (dd, J = 8.7, 1.3 Hz, 1 H, H 8'), 7.70 (ddd, J = 8.5, 6.9, 1.3 Hz, 1 H, H 6'), 7.59 (d, J = 8.5 Hz, 1 H, H 5'), 7.29 (ddd, J = 8.7, 6.9, 1.3 Hz, 1 H, H 7'), 6.33 (br s, 1 H, NH), 5.22 (s, 1 H, CONH), 3.51 (q, J = 6.9 Hz, 2 H, H 1), 3.38 (q, J = 6.8 Hz, 2 H, H 6), 1.66-1.73 (m, 2 H, H 5), 1.59-1.65 (m, 2 H, H 2), 1.40-1.47 (m, 4 H, H 3, H 4); ^{13}C NMR δ 158.7, 156.8 (q, J = 37 Hz), 148.6, 135.0, 130.2, 126.0, 124.1, 119.8, 115.7 (q, J = 288 Hz), 40.6, 39.2, 28.6, 28.2, 25.9, 25.8; Anal. calc. for $C_{15}H_{18}F_3N_5O_2$: C, 50.4; H, 5.1; N, 19.6; found: C, 50.7; H, 4.9; N, 19.6%, and:

(ii) *N*-{6-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]hexyl}-2,2,2-trifluoroacetamide (**10**) (346 mg, 22%) as a red solid, mp (MeOH/DCM) 163-165 °C; IR (KBr) υ 3437, 3266, 1699, 1634, 1178 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 9.42 (s, 1 H, NH), 8.31 (t, J = 6.0 Hz, 1 H, CONH), 8.20 (d, J = 8.7 Hz, 1 H, H 8'), 8.12 (d, J = 8.6 Hz, 1 H, H 5'), 7.91-7.95 (m, 1 H, H 6'), 7.53-7.57 (m, 1 H, H 7'), 3.40 (q, J = 6.7 Hz, 2 H, H 1), 3.18 (q, J = 6.6 Hz, 2 H, H 6), 1.58-1.64 (m, 2 H, H 2), 1.46-1.53 (m, 2 H, H 5), 1.28-1.38 (m, 4 H, H 3, H 4); ^{13}C NMR [$(CD_3)_2SO$] δ 156.0 (q, J = 36 Hz), 149.7, 138.1, 135.4, 129.8, 126.7, 121.1, 116.8, 115.9 (q, J = 288 Hz), 40.5, 39.0, 28.5, 28.1, 25.8, 25.7; Anal. calc. for $C_{15}H_{18}F_3N_5O_3$: C, 48.3; H, 4.9; N, 18.8; found: C, 48.5; H, 4.7; N, 18.0%.

Oxidation of 2,2,2-trifluoro-*N*-{6-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]hexyl}acetamide (9). Trifluoroacetic anhydride (4.0 mL, 28.6 mmol) was added dropwise to a stirred suspension of 35% H_2O_2 (2.2 mL, ca. 23 mmol) in DCM (20 mL) at 5 °C and the mixture was stirred for 15 min. The mixture was dried and added to a stirred solution of 1-oxide **9** (409 mg, 1.14 mmol) in DCM (50 mL) and the solution stirred at 20 °C for 48 h. The solution was partitioned between sat. aq. $KHCO_3$ (50 mL) and $CHCl_3$ (50 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 40 mL), the combined organic fraction dried, and the solvent evaporated (CAUTION). The residue was chromatographed, eluting with a gradient (0-10%) MeOH/(40-0%) EtOAc/DCM, to give (i) starting material **9** (250 mg, 61%); and (ii) 1,4-dioxide **10** (124 mg, 29%), spectroscopically identical to a sample obtained above.

***N*^{1}-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (7).** 1 M NaOH solution (2.8 mL, 2.8 mmol) was added to a stirred solution of trifluoroacetamide **10** (209 mg, 0.56 mmol) in MeOH (20 mL) and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between sat. aq. $KHCO_3$ (70 mL) and $CHCl_3$ (70 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 30 mL), the combined organic fraction dried, and the solvent evaporated to give amine **7** (129 mg, 83%), spectroscopically identical with the sample obtained above.

Example B.

***N*^{1}-(9-Acridinyl)-*N*^{6}-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,6-hexanediamine (11).** A solution of amine **7** (64 mg, 0.23 mmol) and 9-methoxyacridine (53 mg, 0.25 mmol) in MeOH (10 mL) was stirred at reflux temperature for 10 h. The solvent was evaporated and the residue chromatographed on neutral alumina, eluting with a gradient (0-5%) of MeOH/$CHCl_3$, to give compound **11** (63 mg, 60%) as a red solid, IR (KBr) υ 3293, 1593, 1414, 1362 cm^{-1}; ^{1}H NMR δ 8.30 (d, J = 8.5 Hz, 1 H, H 8"), 8.29 (d, J = 8.5 Hz, 1 H, H 5"), 8.11 (d, J = 8.6 Hz, 2 H, H 1', H 8'), 8.04 (d, J = 8.6 Hz, 2 H, H 4', H 5'), 7.84 (ddd, J = 8.5, 7.2, 1.2 Hz, 1 H, H 6"), 7.59-7.64 (m, 2 H, H 3', H 6'), 7.57 (ddd, J = 8.5, 7.2, 1.2 Hz, 1 H, H 7"), 7.31-7.35 (m, 2 H, H 2', H 7'), 7.15 (br s, 1 H, NH), 3.84 (dd, J = 7.2, 7.1 Hz, 2 H, CH_2N), 3.57 (dt, J = 6.7, 6.5 Hz, 2 H, CH_2N), 1.78-1.85 (m, 2 H, CH_2), 1.67-1.74 (m, 2 H, CH_2), 1.43-1.53 (m, 4 H, 2 ×

CH_2), NH not observed; ^{13}C NMR δ 151.9 (2), 149.8, 148.0, 138.1, 135.8, 130.3, 130.2 (2), 128.1 (2), 127.1, 123.0 (2), 122.9 (2), 121.6, 117.2, 116.1 (2), 50.4, 41.2, 31.4, 29.2, 26.4, 26.3; MS (FAB^+) *m/z* 455 (MH^+, 20%), 439 (10); HRMS (FAB^+) calc. for $C_{26}H_{27}N_6O_2$ (MH+) *m/z* 455.2196, found 455.2182. The compound was dissolved in MeOH and treated with HCl gas and the solvent evaporated. The residue was crystallized from MeOH/EtOAc to give the hydrochloride of **11**, mp (MeOH/EtOAc) 118-119 °C; Anal. calc. for $C_{26}H_{26}N_6O_2 \cdot 2HCl \cdot ½H_2O$: C, 58.2; H, 5.5; N, 15.7; found: C, 57.8; H, 5.5; N, 15.3%.

Example C.

***N*-{6-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]hexyl}-4-acridinecarboxamide (12).** A solution of the amine **7** (447 mg, 1.6 mmol) in THF (20 mL) and DMF (10 mL) was added dropwise to a stirred solution of acridine-4-carboxylic acid imidazolide (440 mg, 1.61 mmol) in THF (20 mL) at 5 °C and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **12** (708 mg, 91%) as a red solid, mp (EtOAc) 196-198 °C; ^1H NMR δ 11.88 (s, 1 H, NH), 8.99 (dd, J = 7.1, 1.5 Hz, 1 H, H 3), 8.90 (s, 1 H, H 9), 8.30 (d, J = 8.4 Hz, 1 H, H 8'), 8.28 (d, J = 8.7 Hz, 1 H, H 5'), 8.17 (d, J = 9.1 Hz, 1 H, H 5), 8.14 (dd, J = 8.4, 1.5 Hz, 1 H, H 1), 8.04 (d, J = 8.1 Hz, 1 H, H 8), 7.84-7.91 (m, 2 H, H 6, H 6'), 7.66 (dd, J = 8.3, 7.2 Hz, 1 H, H 2), 7.59 (ddd, J = 7.9, 7.0, 0.9 Hz, 1 H, H 7), 7.59 (ddd, J = 8.4, 7.2, 1.2 Hz, 1 H, H 7'), 7.11 (br dd, J = 5.7, 5.5 Hz, 1 H, CONH), 3.71 (dd, J = 6.9, 5.6 Hz, 2 H, CH_2N), 3.63 (dd, J = 6.9, 6.7 Hz, 2 H, CH_2N), 1.83-1.89 (m, 2 H, CH_2), 1.74-1.81 (m, 2 H, CH_2), 1.55-1.68 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 164.6, 149.7, 147.0, 145.5, 145.0, 138.7, 138.1, 135.4, 134.5, 132.8, 132.0, 129.8, 128.5, 128.3, 126.8, 126.5, 126.4, 125.6, 125.3, 121.1, 116.8, 40.6, 39.0, 29.0, 29.6, 26.5, 26.0; Anal. calc. for $C_{27}H_{26}N_6O_0 \cdot H_2O$: C, 64.8; H, 5.6; N, 16.8; found: C, 65.0; H, 5.5; N, 17.1%.

Example D.

***N*-{6-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]hexyl}-4-quinolinecarboxamide (13).** A solution of 4-quinolinecarboxylic acid (308 mg, 1.78 mmol) and CDI (346 mg, 2.13 mmol) in DMF (20 mL) were stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallised from DCM/pet. ether to give 4-(1*H*-

imidazol-1-ylcarbonyl)quinoline which was used directly without characterisation. A solution of the amine **7** (494 mg, 1.78 mmol) in DMF (10 mL) was added dropwise to a stirred solution of imidazolide in THF (20 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **13** (619 mg, 80%) as a red powder, mp (MeOH/DCM) 196-198 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.96 (d, J = 4.3 Hz, 1 H, H 2), 8.75 (t, J = 5.5 Hz, 1 H, CONH), 8.32 (t, J = 6.1 Hz, 1 H, NH), 8.20 (d, J = 8.6 Hz, 1 H, H 8"), 8.12 (d, J = 8.6 Hz, 1 H, H 5"), 8.11 (d, J = 8.7 Hz, 1 H, H 5), 8.06 (d, J = 8.4 Hz, 1 H, H 8), 7.92 (ddd, J = 8.4, 7.1, 1.3 Hz, 1 H, H 6"), 7.80 (ddd, J = 8.4, 7.1, 1.0 Hz, 1 H, H 7), 7.66 (ddd, J = 8.5, 7.0, 1.0 Hz, 1 H, H 6), 7.55 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H 7"), 7.52 (d, J = 4.4 Hz, 1 H, H 3), 3.39-3.43 (m, 2 H, H 1'), 3.33-3.35 (m, 2 H, H 6'), 1.65-1.70 (m, 2 H, H 2'), 1.56-1.73 (m, 2 H, H 5'), 1.38-1.45 (m, 4 H, H 3', H 4'); ^{13}C NMR [$(CD_3)_2SO$] δ 166.4, 150.2, 149.7, 147.8, 142.4, 138.1, 135.4, 129.8, 129.6, 129.2, 127.1, 126.7, 125.3, 124.1, 121.0, 118.8, 116.7, 40.6, 38.9, 28.8, 28.6, 26.1, 25.9; Anal. calc. for $C_{23}H_{24}N_6O_3$: C, 63.9; H, 5.6; N, 19.4; found: C, 63.9; H, 5.4; N, 19.5%.

Example E.

***N*-{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}-4-acridinecarboxamide (17).**

***tert*-Butyl 3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propylcarbamate (14).** A solution of chloride **3** (4.0 g, 22.0 mmol), *tert*-butyl 3-aminopropylcarbamate (5.76 g, 33.0 mmol) and Et_3N (4.6 mL, 33.0 mmol) in DCM (150 mL) was stirred at 20 °C for 5 d. The solvent was evaporated, and the residue chromatographed, eluting with 20% EtOAc/DCM, to give 1-oxide **14** (5.21 g, 74%) as a yellow powder, mp (EtOAc/DCM) 145-147 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (dd, J = 8.6, 1.1 Hz, 1 H, H 8'), 7.84 (s, 1 H, NH), 7.78 (ddd, J = 8.4, 7.1, 1.1 Hz, 1 H, H 6'), 7.56 (d, J = 8.4 Hz, 1 H, H 5'), 7.32 (ddd, J = 8.6, 7.1, 1.1 Hz, 1 H, H 7'), 6.83 (t, J = 5.3 Hz, 1 H, $NHCO_2$), 3.32-3.36 (m, 2 H, H 1), 2.99-3.04 (m, 2 H, H 3), 1.66-1.73 (m, 2 H, H 2), 1.37 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.9, 155.6, 148.2, 135.7, 130.0, 125.9, 124.4, 119.9, 77.4, 38.2, 37.5, 28.9, 28.2 (3); Anal. calc. for $C_{15}H_{21}N_5O_3$: C, 56.4; H, 6.6; N, 21.9; found: C, 56.4; H, 6.6; N, 22.1%.

***tert*-Butyl 3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propylcarbamate (15).** A solution of MCPBA (6.74g, 27.3 mmol) in DCM (80 mL) was added dropwise to a stirred solution of 1-oxide **14** (5.82 g, 18.2 mmol) in DCM (300 mL) and $NaHCO_3$ (3.1 g, 36.5 mmol). The mixture was stirred at 20 °C for 1 h, partitioned between DCM (400 mL) and sat. aq. $KHCO_3$ solution (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/40%EtOAc/DCM, to give (i) starting material **14** (2.63 g, 45%) and (ii) 1,4-dioxide **15** (1.47 g, 24%) as a red solid, mp (EtOAc/MeOH) 134-136 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.30 (t, J = 6.2 Hz, 1 H, NH), 8.20 (d, J = 8.5 Hz, 1 H, H 8'), 8.13 (d, J = 8.5 Hz, 1 H, H 5'), 7.93 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H 6'), 7.57 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H 7'), 6.86 (t, J = 5.6 Hz, 1 H, $NHCO_2$), 3.38-3.42 (m, 2 H, H 1), 2.98-3.02 (m, 2 H, H 3), 1.68-1.74 (m, 2 H, H 2), 1.37 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 155.6, 149.7, 138.1, 135.4, 129.8, 126.8, 121.0, 116.8, 77.4, 38.2, 37.1, 28.9, 28.1 (3); Anal. calc. for $C_{15}H_{21}N_5O_4 \cdot ¼EtOAc$: C, 53.8; H, 6.5; N, 19.6; found: C, 53.5; H, 6.5; N, 19.5%.

***N*^{1}-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)-1,3-propanediamine (16).** HCl saturated MeOH (20 mL) was added to a solution of carbamate **15** (1.47 mg, 4.38 mmol) in MeOH (30 mL) and the solution stirred at 20 °C for 16 h. The solution was evaporated and the residue dissolved in water (20 mL) the solution neutralized with $KHCO_3$ and extracted with $CHCl_3$ (5 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give compound **16** (0.82 g, 80%) as a red solid, mp (MeOH) 121-123 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.24 (d, J = 8.4 Hz, 1 H, H 8'), 8.13 (d, J = 8.6 Hz, 1 H, H 5'), 7.99 (ddd, J = 8.6, 7.1, 1.0 Hz, 1 H, H 6'), 7.61 (ddd, J = 8.4, 7.1, 1.0 Hz, 1 H, H 7'), 4.01 (br s, 3 H, NH, NH_2), 3.48 (t, J = 6.7 Hz, 2 H, H 1), 2.66 (t, J = 7.0 Hz, 2 H, H 3), 1.73-1.77 (m, 2 H, H 2); MS (FAB$^+$) *m/z* 236 (MH^+, 6%), 220 (10), 204 (5); HRMS calc. for $C_{10}H_{14}N_5O_2$ (MH^+) *m/z* 236.1148, found 236.1139.

***N*-{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}-4-acridinecarboxamide (17).** A solution of amine **16** (128 mg, 0.54 mmol) in DCM (5 mL) was added dropwise to a stirred solution of 4-(1*H*-imidazol-1-ylcarbonyl)acridine (156 mg, 0.57 mmol) in DCM (10 mL) at 5 °C and the solution was stirred at 20 °C for 6 d. The

solvent was evaporated and the residue chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **17** (102 mg, 80%) as a red gum, ^{1}H NMR [$(CD_3)_2SO$] δ 11.39 (t, J = 5.5 Hz, 1 H, CONH), 9.31 (s, 1 H, H 9), 8.71 (dd, J = 7.1, 1.4 Hz, 1 H, H 3), 8.48 (br s, 1 H, NH), 8.38 (dd, J = 8.4, 1.4 Hz, 1 H, H 1), 8.33 (d, J = 9.2 Hz, 1 H, H 5), 8.22 (d, J = 8.5 Hz, 1 H, H 8), 8.13 (d, J = 8.4 Hz, 1 H, H 8'), 8.06 (d, J = 8.7 Hz, 1 H, H 5'), 7.87-7.95 (m, 2 H, H 6, H 6'), 7.76 (dd, J = 8.4, 7.1 Hz, 1 H, H 2), 7.68 (dd, J = 8.5, 7.2 Hz, 1 H, H 7), 7.54 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H 7'), 3.64-3.70 (m, 4 H, 2 CH_2N), 2.05-2.10 (m, 2 H, CH_2); ^{13}C NMR (CD_3OD) δ 168.9, 152.2, 151.5 (2), 141.0, 140.5, 140.1 (2), 138.8, 137.9, 135.7, 133.7, 131.5, 130.1, 128.9, 128.5, 128.1, 127.0, 123.0, 121.9, 121.6, 40.6, 38.1, 29.6. An analytical sample was recrystallized as the dihydrochloride salt, mp (MeOH/EtOAc) 192 °C; Anal. calc. for $C_{24}H_{20}N_6O_3 \cdot 2HCl \cdot ½H_2O$: C, 55.2; H, 4.4; N, 16.1; found: C, 55.3; H, 4.5; N, 16.1%.

Example F.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-4-acridinecarboxamide (23).**

3-{[2-(2-Hydroxyethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (18). A solution of chloride **3** (3.0 g, 16.52 mmol) in DCM (50 mL) was added to a stirred solution of 2-(aminoethoxy)ethanol (2.49 mL, 24.8 mmol) and Et_3N (3.45 mL, 24.8 mmol) in DCM (80 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with 40% EtOAc/DCM, to give 1-oxide **18** (2.62 g, 63%) as a yellow powder, mp (DCM/EtOAc) 131-131.5 °C; ^{1}H NMR δ 8.25 (dd, J = 8.7, 1.2 Hz, 1 H, H 8), 7.68 (ddd, J = 8.4, 7.2, 1.5 Hz, 1 H, H 6), 7.57 (d, J = 8.4 Hz, 1 H, H 5), 7.28 (ddd, J = 8.7, 7.2, 1.3 Hz, 1 H, H 7), 6.02 (br s, 1 H, NH), 3.74-3.80 (m, 6 H, 3 × CH_2O), 3.64-3.67 (m, 2 H, CH_2N), 2.71 (t, J = 5.9 Hz, 1 H, OH); ^{13}C NMR δ 158.9, 149.7, 135.5, 130.9, 126.4, 124.9, 120.4, 72.4, 69.5, 61.7, 41.9; Anal. calc. for $C_{11}H_{14}N_4O_3$: C, 52.8; H, 5.6; N, 22.4; found: C, 52.9; H, 5.7; N, 22.6%.

3-{[2-(2-Azidoethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (19).

Methanesulfonyl chloride (0.82 mL, 10.6 mmol) was added dropwise to a stirred solution of alcohol **18** (2.41 g, 9.63 mmol) and Et_3N (1.74 mL, 12.5 mmol) in DCM

(100 mL) at 5 °C and the solution stirred at 20 °C for 1 h. The solution was diluted with DCM (100 mL) and washed with water (3 × 50 mL), brine (50 mL), dried and the solvent evaporated. The residue was dissolved in DMF (50 mL) and NaN_3 (0.69 g, 10.6 mmol) added. The mixture was heated at 100 °C for 2 h, cooled to 30 °C and the solvent evaporated. The residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with brine (50 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with 50% EtOAc/pet. ether, to give azide **19** (2.35 g, 89%) as yellow crystals, mp (EtOAc/pet. ether) 102-104 °C; ^{1}H NMR δ 8.27 (dd, J = 8.7, 1.4 Hz, 1 H, H 8), 7.70 (ddd, J = 8.6, 7.1, 1.5 Hz, 1 H, H 6), 7.59 (d, J = 8.6 Hz, 1 H, H 5), 7.29 (ddd, J = 8.6, 7.1, 1.4 Hz, 1 H, H 7), 5.70 (br s, 1 H, NH), 3.71-3.78 (m, 4 H, 2 × CH_2O), 3.69 (dd, J = 5.3, 4.8 Hz, 2 H, CH_2N_3), 3.41 (dd, J = 5.1, 4.9 Hz, 2 H, CH_2N); ^{13}C NMR δ 158.9, 148.7, 135.5, 131.1, 126.5, 125.0, 120.4, 70.0, 69.6, 50.7, 41.1; Anal. calc. for $C_{11}H_{13}N_7O_2$; C, 48.0; H, 4.8; N, 35.6; found: C, 48.3; H, 4.6; N, 35.7%.

3-{[2-(2-*tert*-Butyloxycarbamoylethoxy)ethyl]amino}-1,2,4-benzotriazine 1-oxide (20). Propane-1,3-dithiol (5.7 mL, 57.0 mmol) was added dropwise to a stirred solution of azide **19** (1.57 g, 5.70 mmol) and Et_3N (7.95 mL, 57 mmol) in MeOH (100 mL) under N_2 and the solution heated at reflux temperature for 8 h. The solution was cooled to 30 °C and partitioned between 1 M HCl (100 mL) and Et_2O (100 mL). The aqueous fraction was adjusted to pH 12 with 7 M NaOH solution and extracted with DCM (3 × 50 mL). The organic fraction was dried and the solvent evaporated. The residue was dissolved in THF (100 mL) and a solution of di-*tert*-butyldicarbonate (1.87 g, 8.55 mmol) in THF (50 mL) added dropwise. The solution was stirred at 20 °C for 16 h, the solvent evaporated and the residue chromatographed, eluting with 40% EtOAc/pet. ether, to give carbamate **20** (1.85 g, 93%) as a yellow solid, mp (EtOAc/pet. ether) 134-137 °C; ^{1}H NMR δ 8.26 (dd, J = 8.4, 0.9 Hz, 1 H, H 8), 7.71 (ddd, J = 8.3, 7.1, 1.4 Hz, 1 H, H 6), 7.59 (d, J = 8.3 Hz, 1 H, H 5), 7.29 (ddd, J = 8.4, 7.1, 1.3 Hz, 1 H, H 7), 5.74 (br s, 1 H, NH), 4.93 (br s, 1 H, NH), 3.67-3.73 (m, 4 H, 2 × CH_2O), 3.56 (t, J = 5.2 Hz, 2 H, CH_2N), 3.29-3.36 (m, 2 H, CH_2N), 1.45 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 159.9, 155.9, 148.7, 135.5, 131.0, 126.5, 125.0, 120.4, 79.4, 70.2, 69.2, 41.1, 40.4, 28.4 (3); Anal. calc. for $C_{16}H_{23}N_5O_4$: C, 55.0; H, 6.6; N, 20.1; found: C, 55.3; H, 6.8; N, 20.1%.

3-{[2-(2-*tert*-Butyloxycarbamoylethoxy)ethyl]amino}-1,2,4-benzotriazine 1,4-dioxide (21). A solution of MCPBA (1.57 g, 6.35 mmol) in DCM (50 mL) was added dropwise to a stirred solution of carbamate **20** (1.85 g, 5.29 mmol) in DCM (100 mL) and $NaHCO_3$ (0.89 g, 10.6 mmol) and the mixture was stirred at 20 °C for 6 h. The suspension was filtered through celite, the solvent evaporated and the residue chromatographed, eluting with a gradient of (0-5%) MeOH/(40-0%) EtOAc/DCM, to give (i) starting material **20** (926 mg, 50%), spectroscopically identical with an authentic sample, and (ii) 1,4-dioxide **21** (702 mg, 40%) as a red solid, mp (EtOAc) 139-140 °C; ^{1}H NMR δ 8.33 (d, J = 8.7 Hz, 1 H, H 8), 8.30 (d, J = 8.7 Hz, 1 H, H 5), 7.88 (ddd, J = 8.7, 7.2, 1.2 Hz, 1 H, H 6), 7.43-7.50 (m, 2 H, H 7, NH), 5.06 (br s, 1 H, NH), 3.78-3.83 (m, 2 H, CH_2O), 3.69 (dd, J = 5.1, 5.0 Hz, 2 H, CH_2O), 3.56 (dd, J = 5.1, 5.0 Hz, 2 H, CH_2N), 3.29-3.36 (m, 2 H, CH_2N), 1.43 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 156.0, 149.8, 138.5, 135.9, 130.6, 129.5, 121.6, 117.4, 79.4, 70.3, 68.9, 41.3, 40.3, 28.3 (3); MS (FAB^+) *m/z* 366 (MH^+, 40%), 350 (5) 310 (20); HRMS (FAB^+) calc. for $C_{16}H_{24}N_5O_5$ (MH^+) *m/z* 366.1777, found 366.1767; Anal. calc. for $C_{16}H_{23}N_5O_5 \cdot ½H_2O$: C, 51.3; H, 6.5; N, 18.7; found: C, 51.3; H, 6.2; N, 16.9%.

3-{[2-(2-Aminoethoxy)ethyl]amino}-1,2,4-benzotriazine 1,4-dioxide (22). Trifluoroacetic acid (1.66 mL, 34.6 mmol) was added dropwise to a stirred solution of 1,4-dioxide **21** (632 mg, 1.73 mmol) in DCM (50 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between sat. aq. $KHCO_3$ solution (100 mL) and $CHCl_3$ (100 mL).The aqueous phase was extracted with $CHCl_3$ (8 × 50 mL), the combined organic fractions dried, and the solvent evaporated. The residue was crystallized from $CHCl_3$ to give the amine **22** (406 mg, 91%) as a red solid, mp ($CHCl_3$) 124 °C (dec.); ^{1}H NMR δ 8.26 (d, J = 8.9 Hz, 1 H, H 8), 8.23 (d, J = 8.9 Hz, 1 H, H 5), 7.79 (dd, J = 8.8, 7.8 Hz, 1 H, H 6), 7.45 (dd, J = 8.9, 7.7 Hz, 1 H, H 7), 3.75 (dd, J = 5.0, 4.8 Hz, 2 H, CH_2O), 3.66 (dd, J = 5.0, 4.9 Hz, 2 H, CH_2O), 3.47 (dd, J = 5.1, 5.0 Hz, 2 H, CH_2N), 2.82 (dd, J = 5.1, 5.0 Hz, 2 H, CH_2N), NH and NH_2 not observed; ^{13}C NMR δ 149.8, 138.3, 135.8, 130.5, 127.2, 121.6, 117.4, 73.0, 68.9, 41.7, 41.3; MS (FAB^+) *m/z* 266 (MH^+, 20%), 250 (5); HRMS (FAB^+) calc. for $C_{11}H_{16}N_5O_3$ (MH^+) *m/z* 266.1253, found 266.1230; Anal. calc. for $C_{11}H_{15}N_5O_3 \cdot ¼H_2O$: C, 49.0; H, 5.8; N, 26.0; found: C, 49.0; H, 5.7; N, 24.7%.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-4-acridinecarboxamide (23).** A solution of the amine **22** (54 mg, 0.20 mmol) in THF (2 mL) was added dropwise to a stirred solution of 4-(1*H*-imidazol-1-ylcarbonyl)acridine (58 mg, 0.21 mmol) in THF (5 mL) at 5 °C and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **23** (93 mg, 97%) as a red solid, mp (EtOAc) 98-100 °C; ^{1}H NMR δ 12.14 (s, 1 H, CONH), 8.96 (dd, J = 7.1, 1.5 Hz, 1 H, H 3'), 8.82 (s, 1 H, H 9), 8.25 (d, J = 8.4 Hz, 1 H, H 8'), 8.16 (d, J = 8.4 Hz, 1 H, H 5'), 8.11-8.13 (m, 2 H, H 1, H 5), 7.94 (d, J = 8.2 Hz, 1 H, H 8), 7.76-7.84 (m, 2 H, H 6, H 6'), 7.66 (dd, J = 8.4, 7.1 Hz, 1 H, H 2), 7.44-7.52 (m, 2 H, H 7, H 7'), 7.36 (br s, 1 H, NH), 3.85-3.95 (m, 8 H, 2 × CH_2O, 2 × CH_2N); ^{13}C NMR δ 166.1, 149.8, 147.2, 146.3, 138.1, 137.6, 135.5, 135.3, 132.4, 131.3, 130.4, 128.8, 128.3, 128.0, 127.1, 126.8, 126.2, 125.8, 125.4, 121.5, 117.3, 70.2, 68.9, 41.1, 39.5; MS (FAB^+) *m/z* 471 (MH^+, 5%), 455 (4); HRMS (FAB^+) calc. for $C_{25}H_{23}N_6O_4$ (MH^+) *m/z* 471.1781, found 471.1790; Anal. calc. for $C_{25}H_{22}N_6O_4 \cdot ½H_2O$: C, 62.6; H, 4.8; N, 17.5; found: C, 63.0; H, 4.7; N, 17.5%.

Example G.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-8-quinolinecarboxamide (24).** A solution of 8-quinolinecarboxylic acid (308 mg, 1.78 mmol) and CDI (346 mg, 2.13 mmol) in DMF (20 mL) were stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallised from DCM/pet. ether to give 4-(1*H*-imidazol-1-ylcarbonyl)quinoline (50 mg, 0.21 mmol) which was used directly without characterisation. A solution of the amine **22** (57 mg, 0.21 mmol) in DCM (10 mL) was added dropwise to a stirred solution of imidazolide (50 mg, 0.21 mmol) in DCM (5 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **24** (74 mg, 84%) as a red powder, mp (MeOH/DCM) 168-170 °C; ^{1}H NMR δ 11.51 (br s, 1 H, NH), 9.01 (dd, J = 4.2, 1.9 Hz, 1 H, H 2), 8.85 (dd, J = 7.3, 1.6 Hz, 1 H, H 4), 8.30 (d, J = 8.3 Hz, 1 H, H 8"), 8.23-8.26 (m, 2 H, H 7, H 5"), 7.93 (dd, J = 8.1, 1.5 Hz, 1 H, H 5), 7.86 (ddd, J = 8.4, 7.0, 1.8 Hz, 1 H, H 6"), 7.67 (dd, J = 7.9, 7.5 Hz, 1 H, H 6), 7.46-7.51 (m, 2 H, H 3, H 7"), 7.46 (br s, 1 H, NH), 3.78-3.85 (m, 8 H, 2 × CH_2O, 2 × CH_2N); ^{13}C NMR δ 166.0, 149.8, 149.6,

145.6, 138.3, 137.6, 135.7, 133.8, 131.9, 130.5, 128.7, 128.4, 127.2, 126.4, 121.6, 120.9, 117.4, 70.3, 68.9, 41.4, 39.6; MS (FAB^+) *m/z* 421 (MH^+, 8%), 405 (5), 389 (1); HRMS (FAB^+) calc. for $C_{21}H_{21}N_6O_4$ (MH^+) *m/z* 421.1624, found 421.1615; Anal. calc. for $C_{21}H_{20}N_6O_4 \cdot ½MeOH$: C, 59.2; H, 5.1; N, 19.3; found: C, 59.2; H, 4.8; N, 19.2%.

Example H.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-2-phenyl-1*H*-benzimidazole-4-carboxamide (25).** A solution of 2-phenyl-1*H*-benzimidazole-4-carboxylic acid (396 mg, 1.67 mmol) and CDI (270 mg, 1.67 mmol) in DMF (10 mL) was stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallised from DCM/pet. ether to give 4-(1*H*-imidazol-1-ylcarbonyl)-2-phenyl-1*H*-benzimidazole (309 mg, 0.21 mmol) which was used directly without characterisation. A solution of the amine **22** (56 mg, 0.21 mmol) in DCM (5 mL) was added dropwise to a stirred solution of imidazolide (61 mg, 0.21 mmol) in DCM (5 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **25** (89 mg, 86%) as a red powder, mp (DCM) 203-207 °C; ^1H NMR [$(CD_3)_2SO$] δ 13.30 (br s, 1 H, NH), 10.24 (s, 1 H, NH), 8.18-8.24 (m, 3 H, H 2', H 6', NH), 8.13 (d, J = 8.7 Hz, 1 H, H 8"), 8.04 (d, J = 8.5 Hz, 1 H, H 5"), 7.90-7.94 (m, 1 H, H 6"), 7.87 (d, J = 7.9 Hz, 1 H, H 5), 7.72 (d, J = 7.9 Hz, 1 H, H 7), 7.52-7.58 (m, 3 H, H 3', H 5', H 7"), 7.46-7.48 (m, 1 H, H 4'), 7.34 (t, J = 7.9 Hz, 1 H, H 6), 3.78-3.82 (m, 2 H, CH_2O), 3.74-3.77 (m, 2 H, CH_2O), 3.63-3.78 (m, 4 H, 2 × CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 164.5, 151.7, 149.7, 141.0, 138.0, 135.4, 135.1, 130.4, 129.9, 128.9 (2), 128.8, 126.9, 126.6 (2), 122.5, 122.3, 122.0, 121.0, 116.7, 114.8, 69.1, 68.2, 40.3, 38.8; MS (FAB^+) *m/z* 486 (MH^+, 4%), 470 (2); HRMS (FAB^+) calc. for $C_{25}H_{24}N_7O_4$ (MH^+) *m/z* 486.1890, found 486.1903; Anal. calc. for $C_{25}H_{23}N_7O_4$: C, 61.8; H, 4.8; N, 20.2; found: C, 61.6; H, 4.7; N, 20.0%.

Example I.

***N*-(2-{2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethoxy}ethyl)-2-(4-pyridinyl)-8-quinolinecarboxamide (26).** A solution of 2-(4-pyridinyl)-8-quinolinecarboxylic acid (268 mg, 1.07 mmol) and CDI (173 mg, 1.07 mmol) in DMF (10 mL) were stirred at 50 °C for 1 h. The solvent was evaporated and the residue

recrystallized from DCM/pet. ether to give 8-(1*H*-imidazol-1-ylcarbonyl)-2-(4-pyridinyl)quinoline (238 mg, 0.86 mmol) which was used directly without characterization. A solution of the amine **22** (39 mg, 0.15 mmol) in DCM (5 mL) was added dropwise to a stirred solution of imidazolide (41 mg, 0.15 mmol) in DCM (5 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give compound **26** (51 mg, 70%) as a red powder, mp (DCM) 128-130 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.01 (br s, 1 H, NH), 10.83 (t, J = 5.3 Hz, 1 H, NH), 8.70 (dd, J = 4.5, 1.5 Hz, 2 H, H 3', H 5'), 8.63 (d, J = 8.6 Hz, 1 H, H 7), 8.58 (dd, J = 7.3, 1.5 Hz, 1 H, H 4), 8.23 (d, J = 8.7 Hz, 1 H, H 5), 8.19 (dd, J = 8.7, 1.5 Hz, 1 H, H 8"), 8.09 (dd, J = 4.5, 1.5 Hz, 2 H, H 2', H 6'), 7.95 (d, J = 8.5 Hz, 1 H, H 5"), 7.82-7.90 (m, 2 H, H 3, H 6"), 7.76 (t, J = 8.7 Hz, 1 H, H 6), 7.47 (ddd, J = 8.7, 7.0, 1.6 Hz, 1 H, H 7"), 3.70-3.78 (m, 6 H, 2 × CH_2O, CH_2N), 3.49-3.54 (m, 2 H, CH_2N); MS (FAB^+) *m/z* 498 (MH^+, 10%), 482 (5); HRMS (FAB^+) calc. for $C_{26}H_{24}N_7O_4$ (MH^+) *m/z* 498.1890, found 498.1898; Anal. calc. for $C_{26}H_{23}N_7O_4 \cdot H_2O$: C, 60.7; H, 4.9; N, 22.0; found: C, 60.6; H, 4.9; N, 19.0%.

Example J.

***N*-[3-({3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-4-acridinecarboxamide (30).**

***tert*-Butyl 3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl{3-[(trifluoroacetyl)amino]propyl}carbamate (27).** A solution of chloride **3** (1.34 g, 7.41 mmol) in DCM (50 mL) was added dropwise to a stirred solution of *tert*-butyl bis(3-aminopropyl)carbamate (2.57 g, 11.1 mmol) and Et_3N (1.55 mL, 11.1 mmol) in DCM (200 mL) at 20 °C. The solution was stirred at 20 °C for 3 d. The solvent was evaporated and the residue chromatographed, eluting with 50% EtOAc/acetone, to give a crude oil (2.31 g). Trifluoroacetic anhydride (3.5 mL, 24.3 mmol) was added dropwise to a stirred solution of crude amine in pyridine (50 mL) at 5 °C. The solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (30-50%) of EtOAc/pet. ether, to give trifluoroacetamide **27** (0.51 g, 22%) as a yellow solid, mp (EtOAc/pet. ether) 89-90 °C; ^{1}H NMR δ 8.22-8.26 (m, 2 H, H 8, NH), 7.71 (br dd, J = 8.4, 7.0 Hz, 1 H, H 6), 7.59 (d, J = 8.4 Hz, 1 H, H 5), 7.29 (br dd, J = 8.5, 7.0 Hz, 1 H, H 7), 5.45 (br s, 1 H, NH), 4.12 (br dd, J = 6.6, 6.5 Hz, 2 H, CH_2N), 3.26-3.37 (m, 6 H, 3 × CH_2N), 1.84-

1.95 (m, 2 H, CH_2), 1.71-1.77 (m, 2 H, CH_2), 1.48 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 158.9, 157.3 (q, J = 37 Hz), 156.8, 148.0, 135.6, 130.9, 126.5, 125.1, 120.4, 116 (q, J = 288 Hz), 80.8, 44.5, 43.0, 38.8, 35.8, 29.7, 28.3 (3), 27.1; MS (FAB^+) *m/z* 473 (MH^+, 60%), 457 (10), 373 (100); HRMS (FAB^+) calc. for $C_{20}H_{28}F_3N_6O_4$ (MH^+) *m/z* 473.2124, found 473.2136; Anal. calc. for $C_{20}H_{27}F_3N_6O_4$: C, 50.8; H, 5.8; N, 17.8; found: C, 50.5; H, 5.7; N, 17.8%.

***tert*-Butyl 3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl{3-[(trifluoroacetyl)amino]propyl}carbamate (28)**. A solution of MCPBA (2.12 g, 8.6 mmol) in DCM (50 mL) was added dropwise to a stirred solution of 1-oxide **27** (3.13 g, 6.6 mmol) in DCM (250 mL) and $NaHCO_3$ (1.1 g, 13.2 mmol). The mixture was stirred at 20 °C for 16 h, partitioned between DCM (200 mL) and sat. aq. $KHCO_3$ solution (100 mL). The organic fraction was dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-4%) MeOH/40%EtOAc/DCM, to give (i) starting material **27** (2.04 g, 65%) and (ii) 1,4-dioxide **28** (252 mg, 8 %) as a red solid, ^1H NMR δ 8.34 (d, J = 8.7 Hz, 1 H, H 8), 8.30 (d, J = 8.4 Hz, 1 H, H 5), 8.25 (br s, 1 H, NH), 7.88 (br dd, J = 8.4, 7.0 Hz, 1 H, H 6), 7.52 (br dd, J = 8.7, 7.0 Hz, 1 H, H 7), 7.20 (br s, 1 H, NH), 3.62 (dt, J = 6.8, 6.7 Hz, 2 H, CH_2N), 3.26 –3.38 (m, 6 H, 3 × CH_2N), 1.92-1.98 (m, 2 H, CH_2), 1.73-1.79 (m, 2 H, CH_2), 1.49 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 157.3 (q, J = 37 Hz), 156.8, 149.8, 138.2, 135.9, 130.5, 127.4, 121.7, 117.4, 116.1 (q, J = 288 Hz), 80.9, 44.4, 43.2, 38.9, 31.9, 29.7, 28.4 (3), 22.7; MS (FAB^+) *m/z* 489 (MH^+, 10%), 473 (12), 373 (15); HRMS (FAB^+) calc. for $C_{20}H_{28}F_3N_6O_5$ (MH^+) *m/z* 489.2073, found 489.2086.

***tert*-Butyl 3-aminopropyl{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}carbamate (29)**. A mixture of trifluoroacetamide **28** (541 mg, 1.11 mmol) and K_2CO_3 (0.77 g, 5.54 mmol) in MeOH (20 mL) and water (5 mL) was heated at reflux temperature for 1 h. The mixture was partitioned between $CHCl_3$ (50 mL) and water (30 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 30 mL), the combined organic fraction dried, and the solvent evaporated to give amine **29** (322 mg, 74%) as a red oil, ^1H NMR [$(CD_3)_2SO$] δ 10.50 (br s, 1 H, NH), 8.21 (d, J = 8.7 Hz, 1 H, H 8), 8.13 (d, J = 8.6 Hz, 1 H, H 5), 7.94 (br dd, J = 8.6, 7.5 Hz, 1 H, H 6), 7.56 (br dd, J = 8.6, 7.5 Hz, 1 H, H 7), 7.20 (br s, 2 H, NH_2), 3.39 (t, J = 6.9 Hz, 2 H,

CH_2N), 3.11-3.21 (m, 6 H, 3 × CH_2N), 1.78-1.86 (m, 2 H, CH_2), 1.49-1.58 (m, 2 H, CH_2), 1.39 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 154.7, 149.7, 138.1, 135.4, 129.8, 127.9, 121.0, 116.7, 78.3, 44.3, 43.9, 38.8, 38.4, 32.2, 31.6, 27.9 (3); MS (FAB^+) *m/z* 393 (MH^+, 15%), 377 (9), 338 (3); HRMS (FAB^+) calc. for $C_{18}H_{29}N_6O_4$ (MH^+) *m/z* 393.2250, found 393.2249.

***N*-[3-({3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-4-acridinecarboxamide (30).** A solution of 4-acridinecarboxylic acid (846 mg, 4.35 mmol) and CDI (846 mg, 5.21 mmol) in DMF (20 mL) were stirred at 50 °C for 1 h. The solvent was evaporated and the residue recrystallized from DCM/pet. ether to give 4-(1*H*-imidazol-1-ylcarbonyl)acridine (746 mg, 63%) which was used directly without characterization. A solution of the amine **29** (320 mg, 0.82 mmol) in DCM (10 mL) was added dropwise to a stirred solution of imidazolide (234 mg, 0.86 mmol) in THF (25 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-5%) of MeOH/DCM, to give *tert*-butyl 3-[(4-acridinylcarbonyl)amino]propyl{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}carbamate (330 mg, 67%) as a red gum, ^1H NMR δ 11.92 (br s, 1 H, CONH), 8.98 (dd, J = 7.2, 1.5 Hz, 1 H, H 3), 8.89 (s, 1 H, H 9), 8.26-8.32 (m, 3 H, H 5, H 5', H 8'), 8.16 (d, J = 8.3 Hz, 1 H, H 1), 8.07 (d, J = 8.8 Hz, 1 H, H 8), 7.82-7.89 (m, 3 H, H 3, H 6, H 6'), 7.65-7.69 (m, 1 H, H 7'), 7.58-7.62 (m, 1 H, H 7), 7.48 (br s, 1 H, NH), 3.72 (dt, J = 6.6, 6.0 Hz, 2 H, CH_2N), 3.61 (dt, J = 6.6, 6.4 Hz, 2 H, CH_2N), 3.38-3.50 (m, 4 H, 2 × CH_2N), 2.04-2.08 (m, 2 H, CH_2), 1.88-1.94 (m, 2 H, CH_2), 1.40 [s, 9 H, $C(CH_3)_3$]; MS (FAB^+) *m/z* 598 (MH^+, 8%), 582 (6); HRMS (FAB^+) calc. for $C_{32}H_{36}N_7O_5$ (MH^+) *m/z* 598.2778, found 598.2772.

HCl saturated MeOH (30 mL) was added to a solution of carbamate (328 mg, 0.55 mmol) in MeOH (30 mL) and the solution stirred at 20 °C for 16 h. The solution was evaporated and the residue dissolved in water (20 mL) the solution neutralized with $KHCO_3$ and extracted with $CHCl_3$ (5 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give compound **30** (247 mg, 90%) as a red solid, ^1H NMR [$(CD_3)_2SO$] δ 11.38 (t, J = 5.5 Hz, 1 H, CONH), 10.50 (br s, 1 H, NH), 9.28 (s, 1 H, H 9), 8.71 (dd, J = 7.1, 1.5 Hz, 1 H, H 3), 8.35 (dd, J = 8.4, 1.5 Hz, 1 H, H 1), 8.24 (d, J = 8.7 Hz, 1 H, H 5), 8.19 (d, J = 8.3 Hz, 1 H, H 8), 8.14 (d, J = 8.5 Hz, 1 H,

H 8'), 8.03 (d, J = 8.5 Hz, 1 H, H 5'), 7.92-7.96 (m, 1 H, H 6), 7.83-7.88 (m, 1 H, H 6'), 7.75 (dd, J = 8.3, 7.1 Hz, 1 H, H 2), 7.65-7.68 (m, 1 H, H 7), 7.48-7.54 (m, 1 H, H 7'), 7.38 (s, 1 H, NH), 3.64 (dt, J = 6.9, 5.9 Hz, 2 H, CH_2N), 3.46 (t, J = 6.7 Hz, 2 H, CH_2N), 2.79 (t, J = 6.9 Hz, 2 H, CH_2N), 2.70 (t, J = 6.5 Hz, 2 H, CH_2N), 1.88-1.94 (m, 2 H, CH_2), 1.76-1.82 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.7, 149.6, 147.0, 145.4, 138.5, 138.0, 135.3, 134.4, 132.6, 131.8, 129.7, 128.5, 128.4, 128.3, 126.7, 1264.4, 126.3, 125.5, 125.2, 121.0, 116.7, 47.1, 46.9, 39.6, 37.2, 29.3, 28.2; MS (FAB^+) *m/z* 498 (MH^+, 15%), 482 (5); HRMS (FAB^+) calc. for $C_{27}H_{28}N_7O_3$ (MH^+) *m/z* 498.2254, found 498.2258; Anal. calc. for $C_{27}H_{27}N_7O_3 \cdot 2H_2O$: C, 60.8; H, 5.9; N, 18.4; found: C, 60.7; H, 5.6; N, 17.1%.

Example K.

***N*-[3-({3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-1-phenazinecarboxamide hydrochloride (31).** A solution of the amine **29** (223 mg, 0.57 mmol) in THF (10 mL) was added dropwise to a stirred solution of 1-(1*H*-imidazol-1-ylcarbonyl)phenazine (171 mg, 0.63 mmol) in THF (25 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-3%) of MeOH/DCM, to give *tert*-butyl 3-[(1-phenazinecarbonyl)amino]propyl{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}carbamate (137 mg, 40%) as a red gum; ^1H NMR δ 11.22 and 11.06 (2 × s, 1 H, CONH), 9.03 (dd, J = 7.1, 1.4 Hz, 1 H, H 2), 8.64 and 8.27 (2 × s, 1 H, NH), 8.42 (d, J = 8.2 Hz, 1 H, H 9), 8.29-8.37 (m, 3 H, H 4, H 6, H 8'''), 7.86-8.03 (m, 5 H, H 3, H 7, H 8, H 5''', H 6'''), 7.49-7.56 (m, 1 H , H 7'''), 3.69-3.77 (m, 2 H, CH_2N), 3.63-3.68 (m, 2 H, CH_2N), 1.93-2.10 (m, 4 H, 2 × CH_2N), 1.67 and 1.63 [2 × s, 9 H, $C(CH_3)_3$], 1.45-1.53 (m, 4 H, 2 × CH_2); MS (FAB^+) *m/z* 599 (MH^+, 12%), 583 (3); HRMS (FAB^+) calc. for $C_{31}H_{35}N_8O_5$ (MH^+) *m/z* 599.2730, found 599.2733. HCl saturated MeOH (5 mL) was added to a solution of carbamate (135 mg, 0.23 mmol) in MeOH (20 mL) and the solution stirred at 20 °C for 16 h. The solution was evaporated and the residue dissolved in water (20 mL) the solution neutralized with dil. aq. NH_3 and extracted with $CHCl_3$ (5 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give compound **31** (97 mg, 85%) as a red solid, which was converted to the HCl salt and recrystallized, mp (MeOH/EtOAc) 163-169 °C; ^1H NMR [$(CD_3)_2SO$] δ 10.29 (t, J = 5.8 Hz, 1 H, CONH), 9.26 (br s, 2 H,

$NH_2^+Cl^-$), 8.97 (t, J = 6.1 Hz, 1 H, NH), 8.59 (dd, J = 9.0, 2.0 Hz, 1 H, H 2), 8.55 (dd, J = 9.0, 2.0 Hz, 1 H, H 9), 8.41 (dd, J = 8.7, 1.3 Hz, 1 H, H 4), 8.28 (dd, J = 7.9, 2.0 Hz, 1 H, H 6), 8.19 (d, J = 8.2 Hz, 1 H, H 8'''), 7.98-8.08 (m, 5 H, H3, H 7, H 8, H 5''', H 6'''), 7.60 (ddd, J = 8.7, 7.1, 1.4 Hz, 1 H, H 7'''), 3.65-3.69 (m, 2 H, H'), 3.55-3.59 (m, 2 H, H 3''), 3.04-3.13 (m, 4 H, H 3', H 1''), 2.03-2.15 (m, 4 H, H 2', H 2''); ^{13}C NMR [$(CD_3)_2SO$] δ 164.8, 149.8, 142.6, 142.5, 141.3, 139.9, 137.5, 136.5, 133.4, 132.6, 131.8, 131.6, 131.0, 130.5, 130.2, 129.5, 129.0, 127.5, 121.8, 116.2, 44.6, 44.2, 38.1, 36.4, 25.9, 25.1; Anal. calc. for $C_{26}H_{27}ClN_8O_3$ MeOH: C, 57.2; H, 5.5; N, 19.8; found: C, 57.3; H, 5.8; N, 20.0%.

Example L

***N*-[3-({3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]-9-methyl-1-phenazinecarboxamide hydrochloride (32).** A solution of the amine **29** (265 mg, 0.68 mmol) in THF (10 mL) was added dropwise to a stirred solution of 1-(1*H*-imidazol-1-ylcarbonyl)-9-methylphenazine (214 mg, 0.74 mmol) in THF (25 mL) at 5 °C and the solution was stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (5-10%) of MeOH/DCM, to give *tert*-butyl 3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl(3-{[(9-methyl-1-phenazinyl)carbonyl]amino}propyl)carbamate (168 mg, 40%) as a red gum, MS (FAB$^+$) *m/z* 613 (MH^+, 20%), 597 (5), 513 (15), 497 (5); HRMS (FAB$^+$) calc. for $C32H37N_8O_5$ (MH^+) *m/z* 613.2887, found 613.2881.

HCl saturated MeOH (5 mL) was added to a solution of carbamate (168 mg, 0.27 mmol) in MeOH (20 mL) and the solution stirred at 20 °C for 16 h. The solution was evaporated and the residue dissolved in water (20 mL) the solution neutralized with dil. aq. NH_3 and extracted with $CHCl_3$ (5 × 50 mL). The combined organic fraction was dried and the solvent evaporated to give compound **32** (121 mg, 86%) as a red solid, which was converted to the HCl salt and recrystallized, mp (MeOH/EtOAc) 183-186 °C; ^1H NMR [$(CD_3)_2SO$] δ 10.45 (t, J = 5.8 Hz, 1 H, CONH), 9.18 (br s, 2 H, $NH_2^+Cl^-$), 8.73 (t, J = 6.2 Hz, 1 H, NH), 8.63 (dd, J = 7.0, 1.4 Hz, 1 H, H 2), 8.39 (dd, J = 8.7, 1.4 Hz, 1 H, H 4), 8.18 (d, J = 8.7 Hz, 1 H, H 8'''), 8.03-8.11 (m, 3 H, H 3, H 5''', H 7), 7.92 (ddd, J = 8.5,7.1, 1.3 Hz, 1 H, H 6'''), 7.87-7.93 (m, 2 H, H 6, H 8), 7.57 (ddd, J = 8.7, 7.1, 1.3 Hz, 1 H, H 7'''), 3.61-3.66 (m, 2 H, H'), 3.51-3.57 (m, 2 H, H 3''), 2.98-3.10 (m, 4 H, H 3', H 1''), 2.86 (s, 3 H, CH_3), 2.08-2.15 (m, 2 H, H 2'), 1.99-2.05 (m, 2 H, H 2''); ^{13}C NMR [$(CD_3)_2SO$] δ 164.5, 149.7, 142.6, 142.3, 140.4, 138.7,

137.7, 136.6, 136.0, 133.7, 132.7, 131.5, 131.2, 130.2, 130.1, 130.0, 127.1, 127.0, 121.0, 116.4, 44.8, 44.7, 37.9, 36.6, 26.2, 25.1, 17.5; MS (FAB^+) *m/z* 513 (MH^+, 20%), 497 (5); HRMS (FAB^+) calc. for $C_{27}H_{29}N_8O_3$ (MH^+) *m/z* 513.2363, found 513.2352.

Example M

***N*-[2-({2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}amino)ethyl]-4-acridinecarboxamide (37).**

***tert*-Butyl bis-(2-aminoethyl)carbamate (33).** Diethylenetriamine (9.9 mL, 96 mmol) was added to a solution of CF_3CO_2Et (22.8 mL, 192 mmol) in dry ether (80 mL) at 5 °C and the reaction mixture was stirred at 20 °C for 20 h. The resulting white precipitate was filtered and washed with cold ether (100 mL), dried under vacuum to give 2,2,2-trifluoro-*N*-[2-({2-[(trifluoroacetyl)amino]ethyl}amino)ethyl]acetamide (17.26 g, 61%), ^1H NMR [$(CD_3)_2SO$] δ 7.26 (br, 2 H, 2 × CONH), 3.43 (br s, 4 H, 2 × CH_2), 2.86 (t, J = 5.8 Hz, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 157.7 (q, J = 37 Hz), 115.8 (q, J = 288 Hz), 47.3 (2), 39.3 (2).

Di-*tert* butyldicarbonate (8.26 g, 37.8 mmol) was added to a solution of acetamide (10.15 g, 34.4 mmol) in THF (100 mL) at 0 °C and the mixture was stirred at 20 °C for 20 h. Saturated aq. NH_4Cl (80 mL) added and the mixture stirred at 20 °C for 5 h. The mixture was extracted with DCM (3 × 50 mL), dried, and the solvent evaporated to give *tert*-butyl bis{2-[(trifluoroacetyl)amino]ethyl}carbamate (13.5 g, 100 %), ^1H NMR [$(CD_3)_2SO$] δ 9.47 (br, 1 H, CONH), 9.40 (br, 1 H, CONH), 3.30 (m, 8 H, 4 × CH_2), 1.38 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 156.4 (q, J = 36 Hz), 154.7, 115.8 (q, J = 288 Hz), 78.9, 45.4, 45.0, 37.7, 37.4, 27.7 (3).

Conc. ammonia (50 mL) was added to a solution of carbamate (14.0 g, 35.5 mmol) in MeOH (100 mL) and heated at reflux temperature for 20 hr. The solvent was evaporated to give diamine **33** as a yellow foam, ^1H NMR [$(CD_3)_2SO$] δ 3.39 (t, J = 6.4 Hz, 4 H, 2 × CH_2), 2.94 (t, J = 6.4 Hz, 4 H, 2 × CH_2), 1.42 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 154.9, 79.9, 45.1 (2), 37.4 (2), 27.9 (3).

Di-*tert*-butyl 2-aminoethyl{2-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]ethyl}dicarbamate (35). A solution of chloride **3** (1.0 g, 5.5 mmol), diamine **33** (4.47 g, 22.0 mmol), and Et_3N (2.24 g, 22 mmol) in DME (20 mL) was

heated at 90 °C for 3 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-4%) of MeOH/DCM to give (i) *tert*-butyl bis{2-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]ethyl}carbamate (0.34 g, 25%), ^{1}H NMR δ 8.17 (br d, J = 8.5 Hz, 2 H, H 8), 7.71-7.62 (m, 2 H, H 6), 7.52 (br d, J = 8.3 Hz, 2 H, H 8), 7.26-7.22 (m, 2 H, H 7), 6.15 (br s, 1 H, NH), 5.95 (br s, 1 H, NH), 3.71 (q, J = 5.8 Hz, 4 H, 2 × CH_2), 3.37 (br s, 4 H, 2 × CH_2), 1.50 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 158.9, 156.3 (2), 148.6 (2), 135.5 (2), 130.9 (2), 126.4 (2), 124.9 (2), 120.3 (2), 80.7, 47.7 (2), 40.9 (2), 28.4 (3); and (ii) crude *tert*-butyl 2-aminoethyl{2-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]ethyl}carbamate **34** (1.38 g, 72 %) as a yellow foam.

Di-*tert*-butyldicarbonate (2.7 g, 12.4 mmol) was added to a solution of carbamate **34** (1.38 g, 4.0 mmol) in THF (50 mL) and the solution stirred at 20 °C for 36 h. Water (100 mL) was added and the mixture stirred at 20 °C for 1 h. The mixture was extracted with DCM (3 × 50 mL), the organic fraction dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-1%) of aq. NH_3/(0-7%) MeOH/DCM, to give carbamate **35** (0.94 g, 52 %) as a yellow powder, mp (DCM/hexane) 160-163 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.14 (dd, J = 8.3, 0.7 Hz, 1 H, H 8), 8.00 and 7.92 (2 × br s, 1 H, CONH), 7.79 (dd, J = 7.5, 1.2 Hz, 1 H, H 6), 7.58 (br d, *J* = 7.5 Hz, 1 H, H 5), 7.34 (dd, J = 7.7, 1.2 Hz, 1 H, H 7), 6.81 (br s, 1 H, NH), 3.43-3.47 (m, 2 H, CH_2), 3.37 (m, 2 H, CH_2), 3.22 (t, J = 6.2 Hz, 2 H, CH_2), 3.03-3.07 (m, 2 H, CH_2), 1.34 [s, 9 H, $C(CH_3)_3$], 1.34 and 1.27 [2 × s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 158.9, 155.5, 154.7,148.2, 135.7, 130.1, 126.0, 124.6, 119.8, 78.4, 77.5, 47.0, 46.2, 38.5, 38.1, 28.1(3), 27.8 (3); Anal. calc. for $C_{21}H_{32}N_6O_5$ C, 56.2; H, 7.2; N, 18.7; found C, 56.5; H, 7.5; N, 18.8%.

Di-*tert*-butyl 2-aminoethyl{2-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}dicarbamate (36). MCPBA (247 mg, 1.0 mmol) was added to a solution of 1-oxide **35** (300 mg, 0.67 mmol) in DCM (10 mL) and the mixture was stirred at 20 °C for 16 h. The mixture was partitioned between dil. aq. NH_3 (50 mL) and DCM (50 mL) and the aqueous fraction extracted with DCM (3 × 30 mL). The combined organic fraction was dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-2%) of MeOH/DCM, to give (i) starting material (188 mg, 62%) and (ii) 1,4-dioxide **36** (122 mg 39%), mp (DCM/hexane) 128-134 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.39 and 8.32 (2 × br s, 1 H, CONH), 8.21 (dd, J

= 8.7, 0.7 Hz, 1 H, H 8), 8.14 (t, J = 8.0 Hz, 1 H, H 5), 7.94 (t, J = 7.6 Hz, 1 H, H 6), 7.57 (t, J = 7.9 Hz, 1 H, H 7), 6.77 (br s, 1 H, NH), 3.50-3.54 (m , 2 H, CH_2), 3.41-3.44 (m, 2 H, CH_2), 3.20 (t, J = 6.5 Hz, 2 H, CH_2), 3.03 (q, J = 5.6 Hz, 2 H, CH_2), 1.33 [s, 9 H, $C(CH_3)_3$], 1.33 and 1.26 [2 × s, 9 H, $C(CH_3)_3$]; ^{13}C NMR [$(CD_3)_2SO$] δ 155.5 154.6, 149.8, 138.1, 135.5, 129.9, 127.0, 121.0, 116.81, 78.6, 77.4, 46.8, 46.1, 38.5, 38.0, 28.8, 27.7; HRMS calc. for $C_{21}H_{33}H_6O_6$ (M^+) *m/z* 465.2462, found 465.2456.

***N*-[2-({2-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]ethyl}amino)ethyl]-4-acridinecarboxamide (37).** A solution of carbamate **36** (252 mg, 0.54 mmol) in HCl saturated MeOH (10 mL) was stirred at 20 °C for 24 h. The solvent was evaporated and the residue partitioned between aq. NH_3 (20 mL) and DCM (50 mL). The aqueous fraction was extracted with DCM (5 × 20 mL) and the combined organic extracts dried. The solvent was evaporated to give N^1-(2-aminoethyl)-N^2-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (109 mg, 76%), ^{1}H NMR δ 8.33 (d, J = 8.7 Hz, 1 H, H 8), 8.30 (d, J = 8.8 Hz, 1 H, H 5), 7.87 (ddd, J = 8.5, 7.1, 1.0 Hz, 1 H, H 6), 7.50 (ddd, J = 8.4, 7.1, 1.2 Hz, 1 H, H 7), 3.70 (t, J = 5.9 Hz, 2 H, CH_2), 2.98 (t, J = 5.9 H, 2 H, CH_2), 2.84 (t, J = 5.6 Hz, 2 H, CH_2), 2.74 (t, J = 5.6 Hz, 2 H, CH_2), NH and NH_2 not observed.

A solution of N^1-(2-aminoethyl)-N^2-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,2-ethanediamine (96 mg, 0.36 mmol) and 4-(1*H*-imidazol-1-ylcarbonyl)acridine (119 mg, 0.43 mmol) in DMF (5 mL) was stirred at 20 °C for 5 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-2%) of aq. NH_3/(0-7%) MeOH/DCM, to give compound **37** (168 mg, 99%) as a red solid, mp (DCM/hexane) 151-154 °C; ^{1}H NMR δ 11.98 (t, J = 5.3 Hz, 1 H, CONH), 8.82 (dd, J = 8.2, 1.4 Hz, 1 H, ArH), 8.81 (s, 1 H, ArH), 8.08-8.17 (m, 4 H, 4 × ArH), 7.97 (d, J = 8.3 Hz, 1 H, ArH), 7.75-7.82 (m, 2 H, 2 × ArH), 7.60 (dd, J = 8.2, 7.2 Hz, 1 H, ArH), 7.54 (ddd, J = 8.3, 7.3, 0.9 Hz, 1 H, ArH), 7.40 (ddd, J = 8.6, 7.2, 1.2 Hz, 1 H, ArH), 3.86 (q, J = 5.8 Hz, 2 H, CH_2), 3.70 (t, J = 5.8 Hz, 2 H, CH_2), 3.17 (q, J = 6.3 Hz, 4 H, 2 × CH_2), 2 × NH not observed; ^{13}C NMR δ 166.5, 149.7, 147.4, 146.2, 138.0, 137.7, 135.6, 135.3, 132.5, 131.4, 130.2, 128.9, 128.0, 126.9 (2), 126.7, 126.3, 125.9, 125.4, 121.5, 117.2, 48.6, 47.8, 40.6, 39.3; HRMS (FAB^+) calc. for $C_{25}H_{24}N_7O_3$ (MH^+) *m/z* 470.1941 found 470.1934; Anal. calc. for $C_{25}H_{23}N_7O_3$ 1½H_2O: C, 60.5; H, 5.3; N, 19.8; found C, 60.5; H, 5.0; N, 20.0%.

Example N

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-4-acridinecarboxamide (41).**

2,2,2-Trifluoro-*N*-[3-(methyl{3-[(1-oxido-1,2,4-benzotriazin-3-yl)amino]propyl}amino)propyl]acetamide (38). A solution of chloride **3** (2.07 g, 11.4 mmol), N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine (3.31 g, 22.8 mmol) and Et_3N (3.2 mL, 22.8 mmol) in DCM (200 mL) was stirred at 20 °C for 2 d. The solvent was evaporated and the residue dissolved in MeCN (150 mL). Ethyl trifluoroacetate (5.4 mL, 45.6 mmol) and water (0.8 mL, 45.6 mmol) added and the solution heated at reflux temperature for 16 h. The solvent was evaporated, and the residue chromatographed, eluting with a gradient (0-1%) Et_3N/(0-10%) MeOH/DCM, followed by further chromatography, eluting with 10% MeOH/DCM, to give 1-oxide **38** (1.89 g, 43%) as a yellow solid, mp (DCM) 111-115 °C; ^{1}H NMR δ 9.04 (br s, 1 H, NH), 8.25 (dd, J = 8.7, 1.4 Hz, 1 H, H 8'), 7.70 (ddd, J = 8.4, 7.1, 1.4 Hz, 1 H, H 6'), 7.57 (d, J = 8.4 Hz, 1 H, H 5'), 7.29 (ddd, J = 8.7, 7.1, 1.1 Hz, 1 H, H 7'), 6.17 (br s, 1 H, NH), 3.58 (dd, J = 6.6, 5.8 Hz, 2 H, CH_2N), 3.49 (br t, J = 6.0 Hz, 2 H, CH_2N), 2.52-2.58 (m, 4 H, 2 × CH_2N), 2.27 (s, 3 H, NCH_3), 1.84-1.90 (m, 2 H, CH_2), 1.75-1.82 (m, 2 H, CH_2); ^{13}C NMR δ 158.9, 157.3 (q, J = 36 Hz), 148.8, 135.6, 130.8, 126.4, 124.9, 120.4, 116.1 (q, J = 288 Hz), 57.1, 56.4, 41.3, 40.3 (2), 26.3, 24.4; MS (FAB$^+$) *m/z* 387 (MH^+, 100%), 371 (8), 338 (30); HRMS (FAB$^+$) calc. for $C_{16}H_{22}F_3N_6O_2$ (MH^+) *m/z* 387.1756, found 387.1765; Anal. calc. for $C_{16}H_{21}F_3N_6O_2 \cdot ½MeOH$: C, 49.2; H, 5.8; N, 20.9; found: C, 49.1; H, 5.5; N, 20.7%.

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-2,2,2-trifluoroacetamide (39).** Trifluoroacetic anhydride (4.13 mL, 29.2 mmol) was added to a stirred solution of 1-oxide **38** (1.13 g, 2.92 mmol) in $CHCl_3$ (50 mL) and the solution stirred at 20 °C for 30 min. The solution was cooled to –10 °C and 70% H_2O_2 (2 mL) (CAUTION) added dropwise. The solution was stirred at 20 °C for 30 d, partitioned between $CHCl_3$ (50 mL) and sat. aq. $KHCO_3$ (50 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 30 mL), the combined organic fraction dried and the solvent evaporated (CAUTION: safety shield). The residue was chromatographed, eluting with 10%

MeOH/DCM, to give (i) starting material **38** (275 mg, 24%) and (ii) 1,4-dioxide **39** (319 mg, 27%) as a red gum, ^{1}H NMR [$(CD_3)_2SO$] δ 9.44 (br s, 1 H, NH), 8.45 (t, J = 5.9 Hz, 1 H, NH), 8.20 (d, J = 8.8 Hz, 1 H, H 8'), 8.12 (d, J = 8.6 Hz, 1 H, H 5'), 7.93 (ddd, J = 8.6, 7.1, 1.2 Hz, 1 H, H 6'), 7.57 (ddd, J = 8.8, 7.1, 1.3 Hz, 1 H, H 7'), 3.42-3.47 (m, 2 H, CH_2N), 3.21-3.25 (m, 2 H, CH_2N), 2.39 (t, J = 6.7 Hz, 2 H, CH_2N), 2.32 (t, J = 6.9 Hz, 2 H, CH_2N), 2.16 (s, 3 H, NCH_3), 1.72-1.80 (m, 2 H, CH_2), 1.61-1.68 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 155.9 (q, J = 36 Hz), 149.7, 138.1, 135.4, 129.8, 126.7, 121.0, 116.7, 115.9 (q, J = 288 Hz), 54.9, 54.6, 41.4, 39.5, 37.6, 25.9, 25.8; MS (FAB$^+$) *m/z* 403 (MH^+, 25%), 387 (5); HRMS (FAB$^+$) calc. for $C_{16}H_{22}F_3N_6O_3$ (MH^+) *m/z* 403.1706, found 403.1695.

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-4-acridinecarboxamide (41).** A solution of trifluoroacetamide **39** (175 mg, 0.44 mmol) and NH_4OH (5 mL) in MeOH (20 mL) was stirred at 30 °C for 4 h. The solvent was evaporated and the residue dried to give N^1-(3-aminopropyl)-N^3-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-N^1-methyl-1,3-propanediamine (**40**) as a red gum, ^{1}H NMR [$(CD_3)_2SO$] δ 8.43 (br s, 1 H, NH), 8.21 (d, J = 8.5 Hz, 1 H, H 8'), 8.13 (d, J = 8.4 Hz, 1 H, H 5'), 7.94 (ddd, J = 8.4, 7.1, 1.2 Hz, 1 H, H 6'), 7.75 (br s, 2 H, NH_2), 7.57 (ddd, J = 8.7, 7.2, 1.3 Hz, 1 H, H 7'), 3.45 (t, J = 6.8 Hz, 2 H, CH_2N), 3.20-3.25 (m, 2 H, CH_2N), 2.88 (dd, J = 7.4, 7.2 Hz, 2 H, CH_2N), 2.40-2.46 (m, 2 H, CH_2N), 2.20 (s, 3 H, NCH_3), 1.77-1.83 (m, 2 H, CH_2), 1.68-1.75 (m, 2 H, CH_2); MS (FAB$^+$) *m/z* 307 (MH^+, 2%), 291 (5); HRMS (FAB$^+$) calc. for $C_{14}H_{23}N_6O_3$ (MH^+) *m/z* 307.1883, found 307.1883. The amine **40** was dissolved in DCM (5 mL) and added to a stirred solution of 4-(1*H*-imidazol-1-ylcarbonyl)acridine (125 mg, 0.46 mmol) in THF (20 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-1%) Et_3N/(0-15%) MeOH/DCM, to give compound **41** (146 mg, 66%) as a red solid, mp (EtOAc/DCM) 169-171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.41 (t, J = 5.3 Hz, 1 H, CONH), 9.31 (s, 1 H, H 9), 8.69 (dd, J = 7.0, 1 4 Hz, 1 H, H 3), 8.43 (t, J = 5.6 Hz, 1 H, NH), 8.38 (d, J = 7.4 Hz, 1 H, H 1), 8.32 (d, J = 8.8 Hz, 1 H, H 5), 8.21 (d, J = 8.4 Hz, 1 H, H 8), 8.16 (d, J = 8.7 Hz, 1 H, H 8'), 8.09 (d, J = 8.7 Hz, 1 H, H 5'), 7.96 (ddd, J = 8.7, 7.1, 1.1 Hz, 1 H, H 6'), 7.91 (dd, J = 8.8, 7.5 Hz, 1 H, H 6), 7.74 (dd, J = 7.4, 7.0 Hz, 1 H, H 2), 7.69 (br dd, J = 8.7, 7.1 Hz, 1 H, H 7'), 7.55 (dd, J

= 8.4, 7.5 Hz, 1 H, H 7), 3.60-3.65 (m, 2 H, CH_2N), 3.42-3.48 (m, 2 H, CH_2N), 3.39 (s, 3 H, NCH_3), 3.00-3.08 (m, 2 H, CH_2N), 2.60-2.68 (m, 2 H, CH_2N), 2.02-2.08 (m, 2 H, CH_2), 1.92-1.98 (m, 2 H, CH_2); MS (FAB^+) *m/z* 512 (MH^+, 25%), 496 (10); HRMS (FAB^+) calc. for $C_{28}H_{30}N_7O_3$ (MH^+) *m/z* 512.2410, found 512.2424.

Example O.

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]propyl}-8-quinolinecarboxamide (42).**

A solution of 8-quinolinecarboxylic acid (90 mg, 0.5 mmol) and CDI (97 mg, 0.6 mmol) in DMF (5 mL) was stirred at 55 °C for 24 h. The solution was diluted with dry benzene (10 mL), Sephadex LH-20 (300 mg) was added and the mixture stirred at 20 °C for 1 h. The mixture was filtered and the solvent evaporated. The residue was dissolved in dry THF (5 mL) and a solution of (**40**) (80 mg, 0.25 mmol) in THF (5 mL) added, and the solution stirred at 20 °C for 70 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient 0-2% aq NH_3/0-8% MeOH/DCM, to give compound **42** (110 mg, 91%) as a red powder, mp (DCM/pet. ether) 119-121 °C; ^1H NMR δ 11.39 (br s, 1 H, CONH), 8.96 (dd, J = 4.3, 1.8 Hz, 1 H, ArH), 8.74 (dd, J = 7.3, 1.5 Hz, 1 H, ArH), 8.34 (dd, J = 8.8, 1.8 Hz, 1 H, ArH), 8.25 (d, J = 8.3 Hz, 1 H, ArH), 8.17 (d, *J* = 8.6 Hz, 1 H, ArH), 7.98 (br s, 1 H, NH), 7.92 (dd, J = 8.1, 1.5 Hz, 1 H, ArH), 7.78 (dd, J = 8.1, 1.1 Hz, 1 H, ArH), 7.62 (t, J = 7.7 Hz, 1 H, ArH), 7.48 (dd, J = 8.3, 1 H, 4.0 Hz), 7.43 (dd, J = 7.9, 1.0 Hz, 1 H, ArH), 3.68-3.73 (m, 4 H, 2 × CH_2), 3.05 (br m, 4 H, 2 × CH_2), 2.67 (s, 3 H, CH_3), 2.25-2.17 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 166.4, 149.7, 149.6, 145.4, 138.2, 137.7, 135.6, 133.6, 132.0, 130.3, 128.5, 128.4, 127.1, 126.4, 121.5, 121.0, 117.3, 54.7, 54.5, 40.6, 39.4, 37.2, 25.5, 24.5; MS (FAB^+) *m/z* 462 (MH^+, 25%), 446 (5); HRMS calc. for $C_{24}H_{28}N_7O_3$ (MH^+) *m/z* 462.2254, found 462.2249; Anal. calc. for $C_{24}H_{27}N_7O_3$: C, 62.5; H, 5.9; N, 21.2; found: C, 62.1; H, 6.0 ; N, 21.2%.

Example P.

***N*-{3-[{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]-propyl}-2-(4-pyridyl)-8-quinolinecarboxamide (43).** A solution of 2-(4-pyridyl)-quinoline-8-carboxylic acid (160 mg, 0.62 mmol) and CDI (150 mg, 0.92 mmol) in DMF (10 mL) was stirred at 55 °C for 24 h. The solution was cooled to 20 °C, diluted

with dry benzene (15 mL), Sephadex LH-20 (300 mg) was added and the mixture stirred at 20 °C for 1 h. The mixture was filtered and the solvent evaporated. The residue was dissolved in dry THF (5 mL) and a solution of (39) (90 mg, 0.33 mmol) in THF (5 mL) added, and the solution stirred at 20 °C for 4 days. The solvent was evaporated and the residue chromatographed, eluting with a gradient 0-2% aq NH_3/0-8% MeOH/DCM, to give compound **43** (160 mg, 94%) as a red powder, mp (DCM/pet. ether) 179-181 °C; ^{1}H NMR δ 11.08 (br s, 1 H, CONH), 8.86 (dd, J = 4.5, 1.6 Hz, 2 H, ArH), 8.78 (dd, J = 7.4, 1.5 Hz, 1 H, ArH), 8.37 (d, J = 8.6 Hz, 1 H, ArH), 8.21 (d, J = 8.6 Hz, 1 H, ArH), 8.10 (d, J = 8.6 Hz, 1 H, ArH), 7.95 (dd, J = 8.2, 1.4 Hz, 1 H, ArH), 7.92-7.90 (m, 4 H, NH, 3 × ArH), 7.98 (ddd, J = 8.6, 7.5, 1.3 Hz, 1 H, ArH), 7.66 (t, J = 7.7 Hz, 1 H, ArH) 7.40 (ddd, J = 8.6, 7.2, 1.2 Hz, 1 H, ArH), 3.74 (q, J = 6.4 Hz, 2H, CH_2), 3.61 (br m, 2 H, CH_2), 2.85 (br m, 2 H, CH_2), 2.81 (br m, 2 H, CH_2), 2.45 (s, 3 H, CH_3), 2.17 (q, J = 7.2 Hz, 2 H, CH_2), 1.98 (br m, 2 H, CH_2); ^{13}C NMR δ 166.1, 154.5, 150.9, 149.7, 146.2, 145.3, 139.0, 138.2, 135.5, 134.4, 131.5, 130.2, 129.4, 127.9, 127.2, 126.9,121.7, 121.5, 118.7, 117.2, 55.3, 55.2, 41.0, 40.1, 37.7, 26.6, 24.7; HRMS (FAB$^+$) calc. for $C_{29}H_{31}N_8O_3$ (MH^+) *m/z* 539.2519, found 539.2527; Anal. calc. for $C_{29}H_{30}N_8O_3 \cdot ½H_2O$: C, 64.7; H, 5.6; N, 20.8; found: C, 64.1; H, 5.7; N, 20.6%.

Example Q.

***N*-{3-[{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]-propyl}-5-methyl-4-acridinecarboxamide (44).** A solution of 5-methylacridine-4-carboxylic acid (0.13 g, 0.55 mmol) and CDI (0.21 g, 1.3 mmol) in DMF (5 mL) was stirred at 55 °C for 24 h. The solution was diluted with dry benzene (10 mL), Sephadex LH-20 (300 mg) was added and the mixture stirred at 20 °C for 1 h. The mixture was filtered and the solvent evaporated. The residue was dissolved in dry THF (5 mL) and a solution of **40** (80 mg, 0.27 mmol) in THF (5 mL) added, and the solution stirred at 20 °C for 70 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient 0-2% aq NH_3/0-8% MeOH/DCM, to give compound **44** (0.13 g, 88%) as a red powder, mp (DCM/pet. ether) 158-162 °C; ^{1}H NMR δ 12.08 (br s, 1 H, CONH), 8.83 (d, J = 6.9 Hz, 1 H, ArH), 8.76 (s, 1 H, NH), 8.06 (t, J = 8.9 Hz, 2 H, ArH), 7.97 (br d, J = 8.4 Hz, 2 H, ArH), 7.83 (d, J = 8.4 Hz, 1 H, ArH), 7.66 (d, J = 6.7 Hz, 1 H, ArH), 7.56-7.63 (m, 2 H, ArH), 7.46 (dd, J = 7.6,

6.5 Hz, 1 H, ArH), 7.30 (d, J = 7.9 Hz, 1 H, ArH), 3.77 (q, J = 6.3 Hz, 2 H, CH_2), 4.83 (br m, 2 H, CH_2), 3.08 (br m, 4 H, 2 × CH_2), 2.83 (s, 3 H, CH_3), 2.67 (br s, 3 H, CH_3), 2.31 (br m, 2 H, CH_2), 2.15(br m, 2 H, CH_2); ^{13}C NMR δ 166.5, 149.6, 146.9, 145.1, 137.9, 137.9, 135.8, 135.3, 135.1, 132.4, 131.2, 130.0, 127.9, 126.8, 126.4, 126.3, 126.2, 125.8, 125.2, 121.3, 117.0, 55.1, 54.5, 40.5, 39.2, 37.4, 26.1, 24.5, 19.0; HRMS (FAB$^+$) calc. for $C_{29}H_{32}N_7O_3$ (MH^+) *m/z* 526.2593, found 526.2582; Anal. calc. for $C_{29}H_{31}N_7O_3.0.5H_2O$: C, 65.2; H, 6.0; N, 18.3; found: C, 65.0; H, 5.8; N, 18.1%.

Example R.

***N*-{3-[{3-[(1,4-Dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}(methyl)amino]-propyl}-9-methyl-4-phenazinecarboxamide (45).** A solution of 9-methylphenazine-4-carboxylic acid (130 mg, 0.53 mmol) and CDI (100 mg, 0.61 mmol) in DMF (5 mL) was stirred at 55 °C for 6 h. The solution was cooled to 20 °C, diluted with dry benzene (10 mL), Sephadex LH-20 (300 mg) was added and the mixture stirred at 20 °C for 1 h. The mixture was filtered and the solvent evaporated. The residue was dissolved in dry THF (5 mL) and a solution of **40** (80 mg, 0.26 mmol) in THF (5 mL) added, and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient 0-2% aq NH_3/0-8% MeOH/DCM, to give compound **45** (130 mg, 90%) as a red powder, mp (DCM/pet. ether) 138-142 °C; ^{1}H NMR δ 11.23 (br s, 1 H, CONH), 8.84 (d, J = 6.6 Hz, 1 H, ArH), 8.29 (d, J = 7.6 Hz, 1 H, ArH), 8.07 (d, J = 8.5 Hz, 1 H, ArH), 8.04 (d, J = 8.5 Hz, 1 H, ArH), 7.98 (d, J = 8.6 Hz, 1 H, ArH), 7.85 (t, J = 7.8 Hz, 1 H, ArH), 7.78-7.71 (m, 3 H, ArH, NH), 6.48 (t, J = 7.6 Hz, 1 H, ArH); 7.31 (t, J = 7.7 Hz, 1 H, ArH), 3.78-3.71 (m, 4 H, 2 × CH_2), 3.15 (br m, 4 H, 2 × CH_2), 2.88 (s, 3 H, CH_3), 2.73 (br s, 3 H, CH_3), 2.32, (br m, 2 H, CH_2), 2.21 (br m, 2 H, CH_2); ^{13}C NMR δ 165.6, 149.6, 143.2, 142.9, 140.7, 139.4, 137.9, 136.4, 135.4, 135.1, 133.7, 131.3, 131.2, 130.1, 129.7, 128.5, 127.7, 127.0, 121.3, 116.9, 54.9, 54.2, 40.2, 38.9, 37.3, 25.7, 24.3, 18.1; Anal. calc. for $C_{28}H_{30}N_8O_3$: C, 63.9; H, 5.9; N, 21.3; HRMS (FAB$^+$) calc. for ($C_{28}H_{31}N_8O_3$) (MH^+) *m/z* 527.2519 found 527.2533; Anal. calc. for $C_{28}H_{30}N_8O_3.1.75H_2O$: C, 60.3; H, 6.0; N, 20.1; found: C, 60.3; H, 5.6; N, 19.6%.

Example S.

***N*-{3-[(3-{[7-(2-Methoxyethoxy)-1,4-dioxido-1,2,4-benzotriazin-3-yl]amino}propyl)(methyl)amino]propyl}-4-acridinecarboxamide (55).**

3-Amino-1,2,4-benzotriazin-7-ol 1-oxide (46). A mixture of 4-amino-3-nitrophenol (5.0 g, 32.4 mmol) and cyanamide (8.2 g, 194.6 mmol) was heated at 100 °C for 10 min. The resulted solution was cooled to 20 °C and c.HCl (15 mL) was added dropwise, and the mixture was heated at 100 °C for 1.5 h, cooled to 20 °C. A solution of 30% NaOH (40 mL) was then added and heated at 100 °C for 1 h. The reaction mixture was cooled to 20 °C, diluted with water (20 mL), and the precipitate was filtered, washed with water (100 mL), diethyl ether (100 mL), and dried to give amine **46** (5.45 g 97%) as a yellow powder, mp > 300 °C [lit. (Friebe et. al. US Patent 5,856,325, Jan 5, 1999) mp (HOAc) >270 °C]; ^{1}H NMR [$(CD_3)_2SO$] δ 10.37 (br s, 1 H, OH), 7.48 (dd, J = 7.7, 2.6 Hz, 1 H, H-6), 7.40-7.37 (m, 2 H, H-5, H-8), 6.96 (br s, 2 H, NH_2).

7-(2-Methoxyethoxy)-1,2,4-benzotriazin-3-amine 1-oxide (47). A mixture of **46** (1.00 g, 5.8 mmol), dry K_2CO_3 (2.40 g, 17.4 mmol) and 2-bromoethyl methyl ether (2.42 g, 17.4 mmol) in DMF (20 mL) was heated at 80 °C for 2 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-3%) MeOH/DCM, to give compound **47** (1.06 g, 77 %) as a yellow powder, mp (DCM/pet. ether) 201-203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.07(d, J = 9.5 Hz, 1 H, H-5), 7.82 (br s, 2 H, NH_2), 7.76 (dd, J = 9.5, 2.6 Hz, 1 H, H-6), 7.50 (d, J = 2.6 Hz, 1 H, H-8), 4.26, (t, J = 4.3 Hz, 2 H, CH_2), 3.72 (t, J = 4.3 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3); Anal. calc. for $C_{10}H_{12}N_4O_5$: C, 50.8; H, 5.1; N, 23.7; found C, 51.1; H, 5.0; N, 23.7%.

3-Hydroxy-7-(2-methoxyethoxy)-1,2,4-benzotriazine 1-oxide (48). A suspension of **47** (1.00 g, 4.2 mmol) in 2 N HCl (32 mL) was cooled to 5 °C and a solution of $NaNO_2$ (0.58 g, 8.5 mmol) in water (1.5 mL) was added over 1 h. More $NaNO_2$ (0.58 g, 8.5 mmol) in water (1.5 mL) was added and the suspension stirred 72 h at 20 °C. The precipitate was filtered and washed with water. The solid was dissolved in 5% aq. NH_3 and filtered. The filtrate was acidified with conc. HCl to give a precipitate which was filtered dried and chromatographed, eluting with 0-5 % MeOH/DCM to give compound **48** (0.68 g, 68 %) as a yellow solid, mp (DCM/pet.ether) 190-192 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.52 (br, 1 H, OH), 7.69 (br s, 1 H, H-8), 7.53 (dd, J = 8.8, 2.8

Hz, 1 H, H-6), 7.33 (d, J = 8.8 Hz, 1 H, H-5), 4.19 (t, J = 4.4 Hz, 2 H, CH_2), 3.68 (t, J = 4.4 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 154.6, 152.9, 131.8, 129.5, 127.4, 117.8, 101.8, 70.0, 67.9, 58.1; Anal. calc. for $C_{10}H_{11}N_3O_4$: C, 50.6; H, 4.2; N, 17.7; found: C, 50.5; H, 4.7; N, 17.7.

3-Chloro-7-(2-methoxyethoxy)-1,2,4-benzotriazine 1-oxide (49). A mixture of **48** (1.00 g, 4.3 mmol) in $POCl_3$ (8 mL) was refluxed for 2 h. Excess reagent was evaporated under vacuum, and ice cold water (50 mL) was added to the residue, then solid Na_2CO_3 (1.0 g) was added portionwise. The resulting precipitate was filtered and chromatographed, eluting with (50-100 %) DCM/pet. ether, to give compound **49** (0.90 g, 83%) as a pale yellow solid, mp (DCM/pet. ether) 121-125 °C; ^1H NMR [$(CD_3)_2SO$] δ 8.00 (d, J = 9.2 Hz, 1 H, H-5), 7.81 (dd, J = 9.2, 2.9 Hz, 1 H, H-6), 7.68 (d, J = 2.8 Hz, 1 H, H-8), 4.35 (t, J = 4.4 Hz, 2 H, CH_2), 3.74 (t, J = 4.4 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3); Anal. calc. for $C_{10}H_{10}ClN_3O_3$: C, 47.0; H, 3.9; N,16.4, Cl, 13.9; found: C, 46.9; H, 4.3; N, 16.4; Cl, 13.7.

N^1-(3-Aminopropyl)-N^3-[7-(2-methoxyethoxy)-1-oxido-1,2,4-benzotriazin-3-yl]-N^1-methyl-1,3-propanediamine (51). A solution of chloride **49** (0.90 g, 3.5 mmol) *tert*-butyl 3-[(3-aminopropyl)(methyl)amino]propylcarbamate (**50**) (1.60 g, 5.25 mmol) and Et_3N (4 ml) in DME (20 mL) was heated to 90 °C for 4 h. The solvent was evaporated, the residue was dissolved in MeOH (10 mL), and treated with methanolic HCl (100 mL). The reaction mixture was stirred at 20 °C for 20 h, the solvent evaporated and the residue partitioned between DCM and dil. aq. NH_3. The aqueous layer was extracted with DCM (4 × 25 mL), the combined extracts dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-2%) aq. NH_3/(0-10%) MeOH/DCM, to give compound **51** (1.25 g, 98%) as a yellow solid, ^1H NMR [$(CD_3)_2SO$] δ 7.68 (br s, 1 H, NH), 7.55-7.52 (m, 1 H, ArH), 7.50-7.47 (m, 2 H, ArH), 4.20 (t, J = 4.4 Hz, 2 H, CH_2), 3.70 (t, J = 4.4 Hz, 2 H, CH_2), 3.34 (br m, 2 H, CH_2), 3.32 (s, 3 H, OCH_3), 2.54 (br t, J = 6.1 H, 2 H, CH_2), 2.35 (t, J = 6.9 Hz, 2 H, CH_2), 2.31 (t, J = 7.2 Hz, 2 H, CH_2), 2.13 (s, 3 H, NCH_3), 1.70 (quin, J = 6.9 Hz, 2 H, CH_2), 1.47 (quin, J = 7.0 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 158.3, 155.3, 144.5, 129.8, 138.3, 127.5, 98.9, 70.0, 67.7, 58.1, 55.0, 54.9, 41.8, 39.9, 39.1, 30.7, 26.2; HRMS (FAB^+) calc. for $C_{17}H_{29}N_6O_3$ (MH^+) *m/z* 365.2301, found 365.2311.

2,2,2-Trifluoro-*N*-{3-[(3-{[7-(2-methoxyethoxy)-1,4-dioxido-1,2,4-benzotriazin-3-yl]amino}propyl)(methyl)amino]propyl}acetamide (52). Ethyl trifluoroacetate (1.2 mL, 9.8 mmol) and H_2O (0.17 mL, 9.8 mmol) were added to a solution of **51** (1.19 g, 3.3 mmol) in CH_3CN and the reaction mixture was heated at reflux for 18 h. The solvent was evaporated and the residue partitioned between aq. Na_2CO_3 solution and DCM. The aqueous layer was extracted with DCM, the combined organic extracts dried and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-5%) MeOH/DCM to give compound **52** (1.3 g, 87%) as a yellow solid, mp (DCM/pet. ether) 117-119 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.43 (br s, 1 H, CONH), 7.66 (br t, J = 5.3 Hz, 1 H, NH), 7.54-7.45 (m, 3 H, ArH), 4.20 (t, J = 4.4 Hz, 2 H, CH_2), 3.70 (t, J = 4.4 Hz, 2 H, CH_2), 3.36-3.27 (m, 2 H, CH_2), 3.30 (s, 3 H, OCH_3), 3.21 (t, J = 7.0 Hz, 2 H, CH_2), 2.37 (t, J = 6.9 Hz, 2 H, CH_2), 2.31 (t, J = 6.9 Hz, 2 H, CH_2), 2.14 (s, 3 H, NCH_3), 1.70 (quin, J = 7.0 Hz, 2 H, CH_2), 1.63 (quin, J = 7.0 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 158.3, 156.5 (q, J = 18 Hz), 155.3,144.5, 129.8, 128.3, 127.5, 115.9 (q, J = 288 Hz), 98.9, 70.0, 67.7, 58.1, 54.8, 54.5, 41.5, 39.0, 37.7, 26.2, 25.8; HRMS (EI$^+$) calc. for $C_{19}H_{27}F_3N_6O_4$ (M^+) *m/z* 460.2046, found 460.2040; Anal. calc. for $C_{19}H_{27}F_3N_6O_4$ C, 49.6; H, 5.9; N, 18.3; F, 12.4; found C, 49.9; H, 5.9; N, 18.2; F, 12.4%.

2,2,2-Trifluoro-*N*-{3-[(3-{[7-(2-methoxyethoxy)-1,4-dioxido-1,2,4-benzotriazin-3-yl]amino}propyl)(methyl)amino]propyl}acetamide (53). 70% H_2O_2 (1.05 mL, 21.7 mmol) was added dropwise to a solution of trifluoroacetic anhydride (3.0 mL, 21.7 mmol) in DCM (10 mL) at 5 °C. The solution was stirred at 5 °C for 10 min, 20 °C for 10 min, and then cooled to 5 °C. The solution was added dropwise to a solution of 1-oxide **52** (1.0 g, 2.2 mmol) and TFA (0.33 mL, 4.3 mmol) in DCM (50 mL). The reaction mixture was stirred at 20 °C for 18 h. The solution was partitioned between aq. $NaHCO_3$ solution and DCM, the aqueous layer extracted further with DCM (5 × 30 mL), the combined extracts dried, and the solvent evaporated. The residue was chromatograped, eluting with a gradient (0-5%) of MeOH/DCM to give compound **53** (0.32 g, 30%) as a red solid, mp (DCM/pet. ether) 91-94 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.43 (br s, 1 H, CONH), 8.24 (t, J = 5.6 Hz, 1 H, NH,), 8.05 (d, J = 9.5 Hz, 1 H, H-5), 7.60 (dd, J = 9.5, 2.7 Hz, 1 H, H-6), 7.50 (d, J = 2.6 Hz, 1 H, H-8), 4.26 (t, J = 4.3 Hz,

2 H, CH_2), 3.72 (t, J = 4.3 Hz, 2 H, CH_2), 3.41 (q, J = 6.6 Hz, 2 H, CH_2), 3.33 (s, 3 H, OCH_3), 3.23 (q, J = 6.3 Hz, 2 H, CH_2), 2.38 (t, J = 6.7 Hz, 2 H, CH_2), 2.32 (t, J = 6.9 Hz, 2 H, CH_2), 2.15 (s, 3 H, NCH_3), 1.75 (quin, J = 6.7 Hz, 2 H, CH_2), 1.65 (quin, J = 6.9 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 157.0, 156.0 (q, J = 6 Hz), 149.0, 134.2, 130.2, 128.2, 120.2, 115.9 (q, J = 279 Hz), 99.5, 69.9, 68.0, 58.1, 54.9, 54.6, 41.5, 39.5, 37.7, 25.9, 25.8; HRMS (FAB^+) calc. for $C_{19}H_{28}F_3N_6O_5$ (MH^+) *m/z* 477.2073, found 477.2074.

***N*-{3-[(3-{[7-(2-Methoxyethoxy)-1,4-dioxido-1,2,4-benzotriazin-3-yl]amino}propyl)(methyl)amino]propyl}-4-acridinecarboxamide (55).** A solution of trifluoroacetamide **53** (1.55 g, 0.33 mmol) and aq. NH_3 (8 mL) in MeOH (10 mL) was stirred at 20 °C for 18 h. The solvent was evaporated and the residue dried to give the intermediate amine **54** as a red solid. The solid was dissolved in dry THF (10 mL) and 4-(1*H*-imidazol-1-ylcarbonyl)acridine (0.18 g, 0.65 mmol) added and solution stirred at 20 °C for 72 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-2 %) aq. NH_3/(0-5 %)MeOH/DCM, to give compound **55** (150 mg, 79%) as a red solid, mp (DCM/pet. ether) 98-103 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.32 (t, J = 5.3 Hz, 1 H, CONH), 9.27 (s, 1 H, NH), 8.68 (dd, J = 7.0, 1.5 Hz, 1 H, ArH), 8.33 (dd, J = 8.4, 1.3 Hz, 1 H, ArH), 8.27- 8.18 (m, 3 H, ArH), 7.96-7.91 (m, 2 H, ArH), 7.72 (dd, J = 8.2, 7.2 Hz, 1 H, ArH), 7.66 (t, J = 7.3 Hz, 1 H, ArH), 7.50 (dd, J = 9.5, 2.6 Hz, 1 H, ArH), 7.40 (d, J = 2.6 Hz, 1 H, ArH), 4.23 (t, J = 4.3 Hz, 2 H, CH_2), 3.71 (t, J= 4.4 Hz, 2 H, CH_2), 3.59 (q, J = 6.4 Hz, 2 H, CH_2), 3.43 (q, J = 6.4 Hz, 2 H, CH_2), 2.56 (t, J = 7.0 Hz, 2 H, CH_2), 2.46 (t, J = 6.7 Hz, 2 H, CH_2), 2.23 (s, 3 H, NCH_3), 1.91 (quin, J = 6.8 Hz, 2 H, CH_2), 1.78 (quin, J = 6.6 Hz, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.6, 156.9, 148.9, 146.9, 145.4, 138.5, 134.3, 134.1, 132.6, 131.8, 130.0, 128.5, 128.3, 128.3, 128.0, 126.4, 126.3, 125.5, 125.1, 118.4, 99.4, 69.9, 68.0, 58.1, 55.2, 55.0, 41.8, 39.7, 37.4, 26.9, 25.8; HRMS (FAB^+) calc. for $C_{31}H_{36}N_7O_5$ (MH^+) *m/z* 586.2778, found 586.2768; Anal. calc. for $C_{31}H_{35}N_7O_5$: C, 63.6; H, 6.0; N, 16.7; found C, 62.3; H, 6.1; N, 16.5%.

Example T.

***N*-{2-[[3-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)propyl](methyl)amino]propyl}-4-acridinecarboxamide (62).**

3-Allyl-1,2,4-benzotriazine 1-oxide (56). $Pd(PPh_3)_4$ (640 mg, 0.55 mmol) was added to a stirred solution of chloride **3** (2.0 g, 11.0 mmol) and allyltributyltin (3.8 mL, 12.1 mmol), the solution degassed, and stirred under N_2 at reflux temperature for 6 h. The solvent was evaporated and the residue chromatographed, eluting with 20% EtOAc/pet. ether to give an oil which was chromatographed, eluting with 5% EtOAc/DCM, to give alkene **56** (1.92 g, 93%) as a white solid, mp (EtOAc/pet. ether) 57-58 °C, ^{1}H NMR δ 8.45 (dd, J = 8.6,1.4 Hz, 1 H, H 8), 8.10 (dd, J = 8.4, 1.4 Hz, 1 H, H 5), 7.94 (ddd, J = 8.4, 7.1, 1.4 Hz, 1 H, H 6), 7.70 (ddd, J = 8.6, 7.1, 1.4 Hz, 1 H, H 7), 6.15-6.24 (m, 1 H, H 2'), 5.31 (dq, J = 17.0, 1.5 Hz, 1 H, H 3'), 5.24 (dq, J = 10.1, 1.5 Hz, 1 H, H 3'), 3.80 (dq, J = 6.8, 1.5 Hz, 2 H, H 1'); ^{13}C NMR δ 165.2, 147.5, 135.6, 133.3, 132.7, 130.1, 128.8, 120.8, 118.5, 41.8; Anal. calc. for $C_{10}H_9N_3O$: C, 64.2; H, 4.85; N, 22.45; found C, 63.85; H, 4.9; N, 22.7%.

3-(3-Hydroxypropyl)-1,2,4-benzotriazine 1-oxide (57). A solution of 9-BBN in THF (13.7 mL, 6.8 mmol) was added to a stirred solution of alkene **56** (1.07 g, 5.7 mmol) in THF (50 mL) and the solution stirred at 20 °C for 1 h. A solution of NaOH (3 M; 2.9 ml, 8.5 mmol), followed by 35% H_2O_2 (2.6 mL, 25.6 mmol) were carefully added and the mixture stirred at 20 °C for 1 h. The mixture was diluted with brine (100 mL), extracted with EtOAc (3 × 100 mL), the combined organic fraction dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (10-50%) EtOAc/DCM, to give alcohol **57** (1.02 g, 87%) as a white solid, mp (EtOAc/pet. ether) 99-100 °C; ^{1}H NMR δ 8.46 (dd, J = 8.7, 1.0 Hz, 1 H, H 8), 7.99 (dd, J = 8.5, 1.2 Hz, 1 H, H 5), 7.93 (ddd, J = 8.5, 7.0, 1.0 Hz, 1 H, H 6), 7.70 (ddd, J = 8.7, 7.0, 1.2 Hz, 1 H, H 7), 3.80 (t, J = 6.1 Hz, 2 H, CH_2O), 3.18 (t, J = 7.3 Hz, 2 H, CH_2), 2.15-2.22 (m, 2 H, CH_2), (OH not observed); ^{13}C NMR δ 166.9, 147.3, 135.7, 133.3, 130.1, 128.6, 120.1, 62.1, 34.1, 30.5; Anal. calc. for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.4 ;N, 20.5; found C, 58.6; H, 5.5; N, 20.5%.

***tert*-Butyl 3-{methyl[3-(1-oxido-1,2,4-benzotriazin-3-yl)propyl]amino}propylcarbamate (58).** MsCl (0.52 mL, 6.7 mmol) was added dropwise to a stirred solution of alcohol 57 (1.06 g, 5.2 mmol) and Et_3N (1.1 mL, 7.8 mmol) in DCM (50 mL) and the solution stirred at 20 °C for 1 h. The solution was diluted with DCM (50 mL), washed with water (2 × 30 mL), dried, and the solvent evaporated. The residue was dissolved in dry DMF (20 mL) and *tert*-butyl 3-

(methylamino)propylcarbamate (Rennard et al. *Org. Lett.*, **2000**, *2*, 2117-2120) (9.7 g, 51.6 mmol) added and the solution stirred at 50 °C for 3 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and aq. $KHCO_3$ solution (100 mL). The organic fraction was washed with water (2 × 50 mL), dried, and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give compound **58** (0.93 g, 48%) as a pale yellow oil, ^{1}H NMR δ 8.45 (dd, J = 8.9, 1.4 Hz, 1 H, H 8), 8.10 (br d, J = 8.3 Hz, 1 H, H 5), 7.93 (ddd, J = 8.3, 7.0, 1.4 Hz, 1 H, H 6), 7.70 (ddd, J = 8.9, 7.0, 1.5 Hz, 1 H, H 7), 5.38 (br s, 1 H, NH), 3.17-3.22 (m, 2 H, CH_2N), 3.07 (dd, J = 7.7, 7.4 Hz, 2 H, CH_2), 2.55-2.60 (m, 2 H, CH_2N), 2.49-2.53 (m, 2 H, CH_2N), 2.28 (s, 3 H, NCH_3), 2.10-2.18 (m, 2 H, CH_2), 1.68-1.73 (m, 2 H, CH_2), 1.42 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 166.7, 156.1, 147.5, 135.6, 133.3, 130.0, 128.7, 120.1, 78.9, 56.7, 55.6, 41.5, 39.3, 34.9, 28.3 (3), 26.6, 25.0; MS (FAB^+) *m/z* 376 (MH^+, 55%), 360 (5); HRMS (FAB^+) calc. for $C_{19}H_{30}N_5O_3$ (MH^+) *m/z* 376.2349, found 376.2345.

2,2,2-Trifluoro-*N*-(3-{methyl[3-(1-oxido-1,2,4-benzotriazin-3-yl)propyl]amino}propyl)acetamide (59). A solution of carbamate 58 (0.51 g, 1.35 mmol) in HCl saturated MeOH (30 mL) was stirred at 50 °C for 3 h. The solvent was evaporated and the residue partitioned between dil. aq. NH_3 (50 ml) and $CHCl_3$ (50 mL). The aqueous fraction was extracted with $CHCl_3$ (3 × 30 mL), the combined organic fraction dried, and the solvent evaporated. The residue was dissolved in MeCN (30 mL) and ethyl trifluoroacetate (0.24 mL, 2.03 mmol) and water (30 μL, 1.5 mmol) added. The solution was stirred at reflux temperature for 16 h, cooled to 20 °C and the solvent evaporated. The residue was chromatographed, eluting with a gradient (0-10%) of MeOH/DCM, to give amide **59** (460 mg, 92%) as a pale yellow oil, ^{1}H NMR [$(CD_3)_2SO$] δ 9.41 (br s, 1 H, CONH), 8.37 (d, J = 8.6 Hz, 1 H, H 8), 8.07 (ddd, J = 8.3, 6.9, 1.4 Hz, 1 H, H 6), 8.02 (dd, J = 8.3, 1.3 Hz, 1 H, H 5), 7.83 (ddd, J = 8.6, 6.9, 1.3 Hz, 1 H, H 7), 3.17-3.22 (m, 2 H, CH_2N), 2.95 (dd, J = 7.6, 7.4 Hz, 2 H CH_2), 2.42 (br t, J = 6.8 Hz, 2 H, CH_2N), 2.33 (br t, J = 6.7 Hz, 2 H, CH_2N), 2.16 (s, 3 H, NCH_3), 1.92-2.00 (m, 2 H, CH_2), 1.57-1.64 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 166.2, 156.0 (q, J = 37 Hz), 146.9, 136.0, 132.8, 130.4, 128.3, 119.5, 115.9 (q, J = 288 Hz), 56.1, 54.4, 41.4, 37.6, 34.2, 25.7, 24.8; MS (EI^+) *m/z* 371 (M^+,

7%), 354 (100); HRMS (EI^+) calc. for $C_{16}H_{20}F_3N_5O_2$ (M^+) *m/z* 371.1569, found 371.1560.

***N*-{3-[[3-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)propyl](methyl)amino]propyl}-2,2,2-trifluoroacetamide (60).** H_2O_2 (0.6 mL, 12.2 mmol) was added dropwise to a stirred solution of trifluoroacetic anhydride (1.7 mL, 12.2 mmol) in DCM (10 mL) at 5 °C. The mixture was stirred at 5 °C for 5 min., warmed to 20 °C for 20 min., cooled to 5 °C, and added to a stirred solution of amide **59** (453 mg, 1.2 mmol) and trifluoroacetic acid (0.19 mL, 2.4 mmol) in $CHCl_3$ (10 mL) at 5 °C. The mixture was stirred at 20 °C for 4 h, diluted with aq. $KHCO_3$ (15 mL), and extracted with $CHCl_3$ (5 × 30 mL). The combined organic fraction was dried, adsorbed on to silica, and the solvent evaporated (CAUTION: use blast shield). The residue was chromatographed, eluting with a gradient (0-10 %) of MeOH/DCM, to give 1,4-dioxide **60** (268 mg, 57%) as a yellow oil, ^1H NMR [$(CD_3)_2SO$] δ 9.40 (br s, 1 H, NHCO), 8.34-8.38 (m, 2 H, H 5, H 8), 8.10 (ddd, J = 8.7, 7.1, 1.2 Hz, 1 , H 6), 7.94 (ddd, J = 8.5, 7.1, 1.3 Hz, 1 H, H 7), 3.16-3.21 (m, 2 H, CH_2N), 3.04 (dd, J = 7.6, 7.4 Hz, 2 H, CH_2), 2.43 (br t, 6.8 Hz, 2 H, CH_2N), 2.32 (br t, J = 6.8 Hz, 2 H, CH_2), 2.14 (s, 3 H, NCH_3), 1.87-1.94 (m, 2 H, CH_2), 155-1.62 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 155.9 (q, J = 37 Hz), 154.7, 139.3, 135.4, 134.4, 131.7, 120.9, 118.8, 115.8 (q, J = 288 Hz), 56.2, 54.3, 41.3, 37.6, 27.6, 25.8, 21.8; MS (FAB^+) *m/z* 388 (MH^+, 25%), 372 (5); HRMS (FAB^+) calc. for $C_{16}H_{21}F_3N_5O_3$ (MH^+) *m/z* 388.1597, found 388.1601.

***N*^{1}-[3-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)propyl]-*N*^{1}-methyl-1,3-propanediamine (61).** Aq. ammonia (5 mL) was added to a stirred solution of amide **60** (169 mg, 0.44 mmol) in MeOH (10 mL) and the solution stirred at 40 °C for 6 h. The solvent was evaporated to give crude amine **61** as a brown oil, ^1H NMR [$(CD_3)_2SO$] δ 8.34-8.39 (m, 2 H, H 5, H 8), 8.14 (ddd, J = 8.6, 7.0, 1.1 Hz, 1 H, H 6), 7.96 (ddd, J = 8.5, 7.0, 1.2 Hz, 1 H, H 7), 7.61 (br s, 2 H, NH_2), 3.04 (dd, J = 7.6, 7.4 Hz, 2 H, CH_2N), 2.85 (br dd, J = 7.4, 7.2 Hz, 2 H, CH_2), 2.45 (br t, J = 6.9 Hz, 2 H, CH_2N), 2.39 (br t, J = 6.7 Hz, 2 H, CH_2N), 2.17 (s, 3 H, NCH_3), 1.88-1.95 (m, 2 H, CH_2), 1.63-170 (m, 2 H, CH_2).

***N*-{3-[[3-(1,4-dioxido-1,2,4-benzotriazin-3-yl)propyl](methyl)amino]propyl}-4-acridinecarboxamide (62).** The crude amine **61** was dissolved in dry THF (10 mL) and 4-(1*H*-imidazol-1-ylcarbonyl)acridine (0.18 g, 0.65 mmol) added and solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-10 %) of MeOH/DCM, to give compound **62** (86 mg, 40%) as a yellow gum, which was converted to the hydrochloride salt, a pale green gum, ^{1}H NMR [$(CD_3)_2SO$] δ 11.29 (br s, 1 H, CONH), 10.90 (br s, 1 H, NH^+Cl^-), 9.38 (s, 1 H, H 9), 8.74 (dd, J = 7.0, 1.0 Hz, 1 H, H 3), 8.47 (d, J = 8.7 Hz, 1 H, H 1), 8.42 (dd, J = 8.4, 1.2 Hz, 1 H, H 5), 8.35 (dd, J = 8.6, 0.7 Hz, 1 H, H 8'), 8.31 (d, J = 8.7 Hz, 1 H, H 8), 8.21 (d, J = 8.4 Hz, 1 H, H 5'), 8.11 (ddd, J = 8.7, 7.0, 1.3 Hz, 1 H, H 6), 7.94-8.10 (m, 2 H, H 2, H 6'), 7.78 (dd, J = 8.7, 7.0 Hz, 1 H, H 7), 7.67-7.71 (m, 1 H, H 7'), 3.65-3.70 (m, 2 H, CH_2N), 3.30-3.37 (m, 2 H, CH_2N), 3.19-3.28 (m, 2 H, CH_2N), 3.09 (t, J = 7.3 Hz, 2 H, CH_2), 2.79 (d, J = 4.8 Hz, 3 H, NCH_3), 2.16-2.27 (m, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 165.3, 153.0, 146.3, 144.7, 139.6, 139.2, 135.5, 134.7, 134.5, 134.0, 133.0, 132.3, 132.0, 128.4, 128.1, 126.6, 126.3, 125.5, 125.3, 120.9, 118.8, 53.7, 52.7, 39.4, 36.4, 26.8, 23.7, 18.8; MS (FAB^+) *m/z* 497 (MH^+, 12%), 481 (3); HRMS (FAB^+) calc. for $C_{28}H_{29}N_6O_3$ (MH^+) *m/z* 497.2301, found 497.2301.

Example U.

***N*-{3-[[3-(1,4-Dioxido-1,2,4-benzotriazin-3-yl)propyl](methyl)amino]propyl}-1-phenazinecarboxamide (63).** Aq. ammonia (5 mL) was added to a stirred solution of amide **60** (61 mg, 0.16 mmol) in MeOH (10 mL) and the solution stirred at 40 °C for 6 h. The solvent was evaporated to give crude amine **61** as a brown oil. The crude amine **61** was dissolved in dry THF (10 mL) and 1-(1*H*-imidazol-1-ylcarbonyl)phenazine (100 mg, 0.36 mmol) added and solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue chromatographed, eluting with a gradient (0-10 %) of MeOH/DCM, to give compound **63** (44 mg, 56%) as a yellow gum, which was converted to the hydrochloride salt and recrystallised, mp (MeOH/EtOAc) 173 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 10.31 (t, J = 5.8 Hz, 1 H, NH), 9.90 (br s, 1 H, NH^+Cl^-), 8.61 (dd, J = 7.1, 1.4 Hz, 1 H, H 2), 8.48 (dd, J = 9.1, 1.4 Hz, 1 H, H 9), 8.42 (dd, J = 8.6, 1.4 Hz, 1 H, H 4), 8.34 (d, J = 8.4 Hz, 1 H, H 6), 8.30 (dd, J = 8.6, 1.1 Hz, 1 H, H 8'), 8.26 (dd, J = 8.3, 1.4 Hz, 1 H, H 5'), 7.93-8.13 (m, 5 H, H

3, H 7, H 8, H 6', H 7'), 3.62-3.67 (m, 2 H, CH_2N), 3.30-3.34 (m, 2 H, CH_2N), 3.22-3.38 (m, 2 H, CH_2N), 3.07-3.11 (m, 2 H, CH_2), 2.82 (br s, 3 H, NCH_3), 2.10-2.22 (m, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 164.8, 153.1, 142.7, 142.5, 141.2, 140.0, 139.2, 135.6, 134.5, 133.5, 132.7, 132.0, 131.9, 131.6, 130.9, 130.3, 129.4, 129.1, 121.0, 118.8, 54.0, 52.9, 39.4, 36.4, 26.7, 23.8, 19.0; MS (FAB^+) *m/z* 498 (MH^+, 20%), 482 (5); HRMS (FAB^+) calc. for $C_{27}H_{28}N_7O_3$ (MH^+) *m/z* 498.2254, found 498.2256.

Example V

3-[(7-Chloro-4-quinolinyl)amino]-*N*-{3-[(1,4-dioxido-1,2,4-benzotriazin-3-yl)amino]propyl}propanamide (65).

A solution of *N*-(7-chloro-4-quinolinyl)-β-alanine (**64**) (Titus et al, *J. Org. Chem.*, **1948**, *13*, 39-62) (303 mg, 1.2 mmol) and CDI (235 mg, 1.5 mmol) in DMF (5 mL) was stirred at 50 °C for 1 h. The solvent was evaporated and the residue crystallised from DCM/pet. ether to give the imidazolide (290 mg, 80%), which was used directly. A solution of N^1-(1,4-dioxido-1,2,4-benzotriazin-3-yl)-1,3-propanediamine (**16**) (92 mg, 390 μmol) and imidazolide (176 mg, 590 μmol) in DMF (10 mL) was stirred at 20 °C for 3 days, the solvent evaporated and the residue recrystallised from hot MeOH to give compound **65** (84 mg, 46%) as a red powder, mp (MeOH) 202 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 8.40 (d, J = 5.4 Hz, 1 H, H 2'), 8.26 (br t, J = 6.2 Hz, 1 H, NH), 8.18-8.12 (m, 2 H, H 5, H 8), 8.13 (d, J = 8.6 Hz, 1 H, H 5'), 7.99 (br t, J = 5.7 Hz, 1 H, NH), 7.93 (ddd, J = 8.6, 7.1, 1.2 Hz, 1 H, H 6), 7.75 (d, J = 2.2 Hz, 1 H, H 8'), 7.56 (ddd, J = 8.6, 7.1, 1.3 Hz, 1 H, H 7), 7.40 (dd, J = 8.6, 2.2 Hz, 1 H, H 6'), 7.37 (br t, J = 5.4 Hz, 1 H, NH), 6.52 (d, J = 5.4 Hz, 1 H, H 3'), 3.49-3.54 (m, 2 H, CH_2N), 3.36-3.41 (m, 2 H, CH_2N), 3.12-3.17 (m, 2 H, CH_2N), 2.47-2.51 (m, 2 H, CH_2), 1.70-1.77 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 170.3, 151.8, 149.7, 149.6, 149.0, 138.1, 135.4, 133.2, 129.8, 127.4, 126.8, 124.0, 123.9, 121.0, 117.4, 116.8, 99.7, 39.0, 38.2, 35.8, 34.3, 28.5; MS (FAB^+) *m/z* 470 (MH^+, 5%), 468 (15), 454 (1), 452 (3): HRMS (FAB^+) calc. for $C_{22}H_{23}{}^{35}ClN_7O_3$ (MH^+) *m/z* 468.1551, found 468.1546; calc. for $C_{22}H_{23}{}^{37}ClN_7O_3$ (MH^+) *m/z* 470.1540, found 470.1535.

Example W: Cytotoxicity of Compounds

Evaluation of the cytotoxicity of compounds by clonogenic assay under aerobic and hypoxic conditions.

Compounds representative of the invention were evaluated under both aerobic and hypoxic conditions in clonogenic assays, using three cell lines: human colon carcinoma HT-29, murine SCCVII, and human lung adenocarcinoma LXFL. Clonogenic survival was determined using aerobic and hypoxic SCCVII cell suspensions. Drug exposures were performed using continuously stirred and gassed single cell suspensions (10^6 cells/mL) at 37 °C, equilibrated with 5% CO_2 in air or N_2 for 60 min before drug addition. After a 60 min drug exposure cells were washed by centrifugation and plated to determine colony formation. Cytotoxicity was measured as the concentration required to reduce plating efficiency to 10% of controls (C_{10}). The hypoxic cytotoxicity ratio was determined as the ratio of the C_{10} values under aerobic and hypoxic conditions. The relative hypoxic toxicity was determined as the ratio of hypoxic TPZ C_{10} to hypoxic BTO C_{10}. The results of these assays are given in Table 1. Abbreviations used in Table 1 are:

C10 = The concentration of drug (in micromolar) to reduce viable cell numbers to 10% of those of control cell cultures grown under the same conditions but not exposed to drug

TPZ = The C10 values for Tirapazamine in the same experiment, used as a positive control

RHT = Relative hypoxic toxicity is defined as the ratio of concentrations of Tirapazamine/test compound to give equal cell killing under hypoxic conditions.

HCR = Hypoxic cytotoxicity ratio is defined as the ratio of drug concentrations under aerobic and hypoxic condition to produce equal cell survival (5%) determined by clonogenic assay

Table 1. Cytotoxicities of compounds of the invention under aerobic and hypoxic conditions in clonogenic assays

HT 29 cells					
compound	**C10 (μM)**			**RHT**	**HCR**
	C10 (hypoxic)	C10 (aerobic)	TPZ (hypoxic)		
11	0.12	10	50	416	83.0
30	0.9	30	70	78	33.0
SCVIII cells					
compound	**C10 (μM)**			**RHT**	**HCR**
	SN (hypoxic)	SN (aerobic)	TPZ (hypoxic)		
11	0.48	9.6	8	16.7	20.0
17	4.8	>30	9.3	1.94	>6.3
30	0.3	6.4	6	20	21.3
41	0.8	42	10	12.5	52.5
44	0.16	>30	9	56.3	>187
43	1.4	14	8	5.7	10
45	0.31	7.4	9	29	23.9
55	1.1	70	11	10	63.6
LXFL cells					
compound	**C10 (μM)**			**RHT**	**HCR**
	SN (hypoxic)	SN (aerobic)	TPZ (hypoxic)		
11	0.04	1.4	18	450	35.0
30	0.4	5	20	50	12.5
40	0.4	20	15	37.5	50

The results of Table 1 clearly show that the compounds of the invention show large increases in cytotoxicity compared with Tirapazamine, while retaining selective killing under hypoxic conditions.

Wherein the foregoing description reference has been made to reagents, or integers having known equivalents thereof, then those equivalents are herein incorporated as if individually set forth.

While this invention has been described with reference to certain embodiments and examples, it is to be appreciated that further modifications and variations may be made to embodiments and examples without departing from the spirit or scope of the invention.

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AUCKLAND UNISERVICES LIMITED and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY

By Their Attorneys
BALDWIN SHELSTON WATERS

Copy for the designated Office (DO/EP) PCT/NZ2003/000210

PATENT COOPERATION TREATY

31

From the INTERNATIONAL BUREAU

PCT

To:

BALDWIN SHELSTON WATERS
P.O. Box 5999,
Wellesley Street,
Auckland
New Zealand

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 06 April 2004 (06.04.2004)	
Applicant's or agent's file reference JC217441/142	**IMPORTANT NOTIFICATION**
International application No. PCT/NZ2003/000210	**International filing date** (day/month/year) 17 September 2003 (17.09.2003)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
BALDWIN SHELSTON WATERS P.O. Box 852 Wellington New Zealand		
	Telephone No. 64 4 472 1094	
	Facsimile No. 64 4 473 6712	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
BALDWIN SHELSTON WATERS P.O. Box 5999, Wellesley Street, Auckland New Zealand		
	Telephone No. (09) 373 3137	
	Facsimile No. (09) 373 2123	
	Teleprinter No.	

3. Further observations, if necessary:
The agent's new address on the demand form has been considered by the International Bureau as a request for the recording of a change under PCT Rule 92bis. In case of disagreement, the International Bureau should be notified immediately.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Miguel CORBEIRA (Fax 338-71-30)
Facsimile No. (41-22) 338.71.30	Telephone No. (41-22) 338 9201

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JC217441-142	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/NZ2003/000210**	International Filing Date *(day/month/year)* 17 September 2003	Priority Date *(day/month/year)* 17 September 2002
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07D 253/10,.401/12, 403/12; A61K 31/53; A61P 35/00		
Applicant AUCKLAND UNISERVICES LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **6** sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **5** sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [X] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application

Date of submission of the demand 18 March 2004	Date of completion of the report 10 January 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **R.L. POOLEY** Telephone No. (02) 6283 2242

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ2003/000210

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-19, 21-118** as originally filed,
pages , filed with the demand,
pages **20** , received on **9 August 2004** with the letter of **9 August 2004**

☒ the claims, pages **119-135, 137,** as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **136, 138-140,** received on **9 August 2004** with the letter of **9 August 2004**

☐ the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ2003/000210

II. Priority

1. [X] This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   [X] copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   [ ] translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. [ ] This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1).

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7, 10-53, 57-60, 62, 63, 67	YES
	Claims	1-6, 8, 9, 54-56, 61, 64-66	NO
Inventive step (IS)	Claims		YES
	Claims	1-67	NO
Industrial applicability (IA)	Claims	1-67	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents were cited in the International Search report:

D1 - Biochemical Pharmacology, Vol. 65(11) 2003, Delahoussaye et al, pages 1807-1815

D2 - Journal of Heterocyclic Chemistry, Vol. 30(2) 1993, Parrick et al, pages 323-327

D3 - Anti-Cancer Drug Design, Vol 10(3) 1995, Mehta et al, pages 227-241

D4 - WO 1991/004028 A

D5 - EP 972517 A

D6 - US 5827850 A

D7 - DD 272591 A

D8 - Journal of Medicinal Chemistry, Vol. 46(1) 2003, Hay et al, pages 169-182

D9 - Chemical Abstracts, Vol 129, Abstract 339530

D10 - Chemical Abstracts, Vol 116, Abstract 187502

D11 - Chemical Abstracts, Vol. 114, Abstract 164101

D12 - Chemical Abstracts, Vol. 112, Abstract 171760

D13 - Chemical Abstracts, Vol. 111, Abstract 3393

NOVELTY (N) Claims 1-6, 8, 9, 54-56, 61, 64-66

Document D1 discloses an analog compound of tirapazamine (SN 26955) wherein the tirapazamine moiety is attached to an acridine chromophore. The acridine chromophore is the same as that defined in Formula VII of claim 2 and targets the drug to DNA. Document D1 also discloses that SN26955 is potent and selective for the killing of hypoxic cells. It is considered that document D1 anticipates the embodiments of claims 1-6, 8, 9, 54-56, 61, 64 and 66.

Documents D2 and D3 disclose TPZ-theophylline compounds (compounds 6 and 3 respectively) that could be considered to fall within the scope of claim 30 due to the uncertain ambit of "DNA-targeting unit" (see Box VIII of this report). However the applicant's submissions indicate that the theophylline moiety would not be a "DNA-targeting unit" as defined in claim 30. In addition, documents D2 and D3 also indicate that these compounds are inactive as radiosensitisers. Accordingly, after consideration of the applicant's submissions, documents D2 and D3 are considered to be no longer relevant for the purposes of novelty and inventive step.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

(i) Claims 1 and 30 lack descriptive support in relation to the DNA-targeting unit. These claims attempt to define these units according to their desired properties rather than the technical features that would achieve these properties (ie the chemical structure of the compounds). The compounds exemplified in the description all contain the units defined in claims 2 and 31. The inclusion of units additional to those of defined in claims 2 and 31 is considered to be speculative and to place an undue experimental burden on the skilled person to determine the units capable of successfully targeting the DNA.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

Documents D4, D5, D6, D7, D8, D9, D12 and D13 are still considered to disclose compounds that fall within the scope of claims 64 and 65. Note that claims 64 and 65 overlap and the provisos incorporated into these claims do not serve to exclude all of the compounds disclosed in these documents. For example, the compounds 3 amino 6 or 7 methoxy-1,2,4-benzotriazine 1,4 dioxide (excluded from claim 64) still fall within the scope of claim 65(wherein X is O, A is methyl and Y_3 is NH_2). Although the provisos added to claims 64 and 65 exclude some of the compounds exemplified in documents D4-D7, it is considered that these documents still provide an enabling disclosure for many compounds that fall within the scope of claims 64 and 65. The disclosure of a patent document is not restricted to compounds that are specifically exemplified and these documents provide directions that enable the skilled person to prepare many other compounds that fall within the scope of these claims. Additionally, these documents also describe specific compounds that fall within the scope of the claims. See for example document D4 at page 15, lines 1-2 (claim 65) and page 21 line 14 (claim 64). Accordingly these documents anticipate both of these claims. Similarly document D9 discloses compounds that still fall within the scope of claim 64, namely compounds having the Registry Numbers 215535-58-3 and 54215-03-01. Documents D8, D12 and D13 disclose compounds that fall within the scope of claim 65 (eg the compounds at Table 1 of document D8 and the 6 and 7 methoxy compounds referred to above). The compounds now claimed in claims 64 and 65 exclude those disclosed in documents D10 and D11 and accordingly these documents are no longer relevant to considerations of novelty.

Note that documents D1 and D8 have been published between the presently claimed priority date and the international filing date. Accordingly, their relevance is dependant on the validity of the claimed priority date. As the priority document does not appear to have been filed (see the indications in Box II) it has been assumed for the purposes of this report that the filing date is the earliest priority date.

INVENTIVE STEP (IS) Claims 1-67

Claims 1-6, 8, 9, 54-56, 61, 64-66: as above

Claims 7, 10-53, 57-60, 62, 63, 67: These claims are considered to define modifications of the compounds and treatments of document D1 that would be obvious to the skilled person on reading document D1 in light of the common general knowledge in the art. For example, the interchange of the DNA targeting unit from position 3 on the benzotriazine to positions 5-8 as defined in claim 30 has been frequently tried with various other substituent groups in order to obtain the maximum therapeutic activity (see for example documents D4-D10 and D13 where such interchanges have been tried with other substituents). Similarly, the combination therapies defined in claims 57-60 would be obvious conjunctive therapies to apply with an agent having activity in killing hypoxic cells, as disclosed for compound SN 26955 in document D1. For example, such combination therapies have been used with similar compounds in documents D4 (see page 30), D5 (see page 4), D6 (see column 4) and D8 (see abstract). Accordingly the embodiments of claims 7, 10-53, 57-60, 62, 63 and 67 are still considered to lack inventive step in light of the disclosures of document D1.

Note also that apart from the known compounds falling within the scope of claims 64 and 65 (see under novelty above), the exclusion of specific compounds from claims 64 and 65 in an attempt to distinguish these claims from documents D4, D5, D6, D7, D8, D9, D12 and D13 would also seem incapable of conferring inventive step on these claims. The 1,2,4 benzotriazine 1,4-dioxide compounds are well known radiosensitisers as evidenced by the above documents. Claims 64 and 65 define a broad range of 1,2,4 benzotriazine 1,4-dioxide compounds that would seem capable of preparation by routine chemical methodologies and that seem to possess similar properties to the specific 1,2,4 benzotriazine 1,4-dioxide compounds that have already been specifically prepared and exemplified in the above documents. Consequently, even if all known compounds were to be somehow excluded from claims 64 and 65, the remaining compounds would seem to be the technical equivalent of such known compounds and claims to these remaining compounds would therefore also lack inventive step.

INDUSTRIAL APPLICABLITY (IA)

Claims 1-67 are considered to possess industrial applicability.

NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2 NR^2 or $N(OH)R^2$ wherein each $R^2$is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3 NR^3 or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, wherein each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, $NR^5{}_2$ or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and

or a pharmacologically acceptable salt thereof;

including the steps of coupling a compound (a) using a palladium reagent to form compound (b) which can then be converted into a compound of XVII′ as defined above;

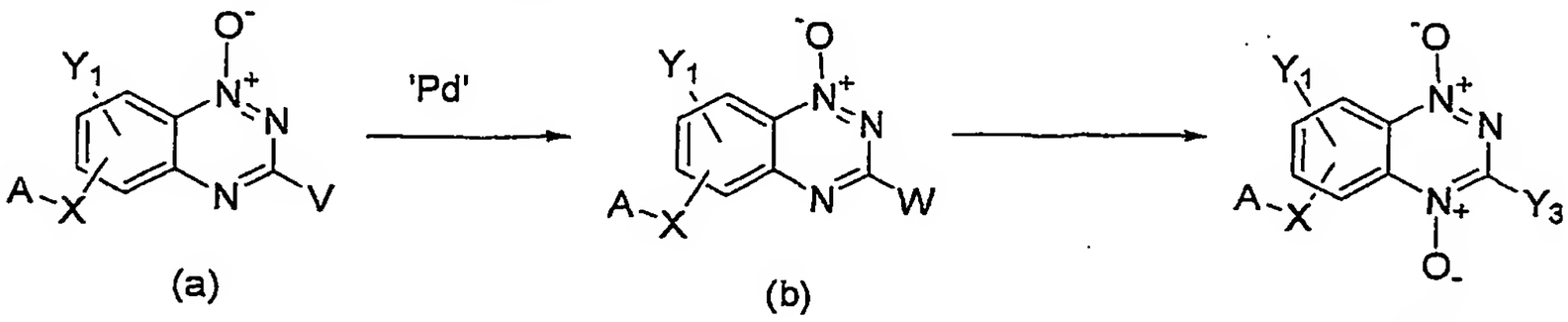
R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2 NR^2 or $N(OH)R^2$ wherein each R^2 isindependently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3 NR^3 or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, wherein each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, $NR^5{}_2$ or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and or a pharmacologically acceptable salt thereof;

including the steps of coupling a compound (a) using a palladium reagent to form compound (b) which is then converted into a compound of XVII' as defined above in this claim;



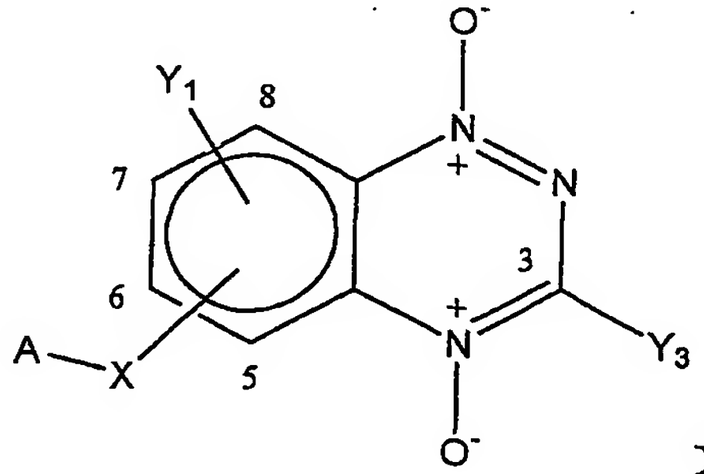
(a) (b) **XVII'**

are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2, or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, wherein each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; or a pharmacologically acceptable salt thereof.

65. A compound of formula XVII'



XVII'

wherein

Y_1 represents at one or more of the available carbons 5-8 on the benzo ring the

following groups: halo, H, R, OH, OR, NO_2, NH_2, NHR, NR_2, SH, SR, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino;

Y_3 is selected from the following groups H, R, OR, NH_2, NHR, NR_2, SO_2R, CF_3, CN, CO_2H, CO_2R, CHO, COR, $CONH_2$, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl and morpholino

wherein each R of groups Y_1 and Y_3 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NO_2, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1, NH_2, NHR^1, NR^1R^1, SH, SR^1, imidazolyl, R^1-piperazinyl, morpholino, SO_2R^1, CF_3, CN, CO_2H, CO_2R^1, CHO, COR^1, $CONH_2$, $CONHR^1$, $CONR^1R^1$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^2, NR^2_2 or $N(OH)R^2$ wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH, and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

A represents an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2, NHR^3, NR^3_2 or $N(OH)R^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN, CO_2H or SH; and wherein the optionally substituted C_{1-12} alkyl chain is optionally interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR^4, CONH, $CONR^4$, NHCO, NR^4CO, wherein each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2, NHR^5, NR^5_2 or $N(OH)R^5$ wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2, NH_2, CF_3, CN,

CO_2H or SH; and

wherein X represents NH, NMe, CH_2, SO, SO_2, or O;

or a pharmacologically acceptable salt thereof.

66. A method of making a compound of Formula I defined above in any one of claims 1 to 29 including the steps of

1 preparing a compound of Formula XVIII as defined above in claim 64; and

2 coupling the compound of Formula XVIII with a DNA targeting agent as defined in claim 2 to provide a compound of Formula I.

67. A method of making a compound of Formula I′ defined in any one of claims 30 to 53 including the steps of

1 preparing a compound of Formula XVII′ as defined above in claim 65; and

2 coupling the compound of Formula XVII′ with a DNA targeting agent as defined above in claim 31 to provide a compound of Formula I′.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ03/00210

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 253/10, 401/12, 403/12; A61K 31/53; A61P 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN Substructure Search based on compounds of Formulae I, I', XVIII and XVII'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Biochemical Pharmacology, Vol. 65 (11), 2003, Delahoussaye et al, "Improved potency of the hypoxic cytotoxin tirapazamine by DNA-targeting", pages 1807-1815 See especially compound SN 26955, page 1808	1-67
X	Journal of Heterocyclic Chemistry, Vol. 30(2), 1993, Parrick et al, "The Synthesis of a Potential Anti-Cancer Agent Containing the Caffeine and 1,2,4-Benzotriazine Moieties", pages 323-327 See especially Compound 6, page 325	30-53, 61, 63, 65,67
X	Anti-Cancer Drug Design, Vol. 10(3), 1995, Mehta et al, "Potential bioreductively activated hypoxia probes and post-irradiation radiosensitizers related to NITP", pages 227-241 See especially Compound 3, page 228	30-53, 61,63,65,67

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
10 December 2003

Date of mailing of the international search report
17 DEC 2003

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ03/00210

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages *(Remove spaces when completed if the page is too long)*	Relevant to claim No.
X	WO 91/04028 A (SRI INTERNATIONAL) 4 April 1991 See especially Examples 6, 10, 11, pages 14-21	64, 65
X	EP 972517 A2 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 19 January 2000 See especially Examples 6, 10, 11, 17, 18	64, 65
X	US 5827850 A (BROWN et al) 27 October 1998 See Column 4, lines 55-60	64, 65
X	DD 272591 A (NICLAS et al) 18 October 1989 See especially Examples 5,6	64, 65
P,X	Journal of Medicinal Chemistry, Vol. 46(1), 2003, Hay et al, "Structure-Activity Relationships of 1,2,4-Benzotriazine 1,4-Dioxides as Hypoxia-Selective Analogues of Tirapazamine", pages 169-182 See table 1, page 172	64, 65
X	Chemical Abstracts, Volume 129, Abstract 339530 (& Anti-Cancer Drug Design, Vol. 13 (6), 1998, Kelson et al, "1,2,4-Benzotriazine 1,4-dioxides. An important class of hypoxic cytotoxins with antitumour activity", pages 575-592) See for example RN 166182-17-8, 166182-18-9, 215034-31-4, 215535-59-4	64, 65
X	Chemical Abstracts, Volume 116, Abstract 187502 (& International Journal of Radiation Oncology, Biology, Physics, Vol. 22(4), 1992, Minchinton et al, "Second generation 1,2,4-benzotriazine 1,4-di-N-oxide bioreductive antitumour agents: pharmacology and activity in vitro and in vivo", pages 701-705)	64, 65
X	Chemical Abstracts, Volume 114, Abstract 164101 (& Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry, Vol 12, 1990, Argyropoulos et al, "Cycloadditions of nitril oxides with benzofuran n-oxides", pages 3277-3287) See RN 132922-33-9, 132922-34-0, 132922-35-1, 132922-36-2	65
X	Chemical Abstracts, Volume 112, Abstract 171760 (& Biochemical Pharmacology, Vol. 39(4), 1990, Tocher et al, "Electrochemical studies and DNA damaging effects of the benzotriazine-N-oxides", pages 781-786) See RN 121135-28-2, 121140-01-0	65
X	Chemical abstracts Volume 111, Abstract 3393 (& International Journal of Radiation Oncology, Biology, Physics, Vol. 16 (4), 1989, Zeman et al, "Structure-activity relationships for benzotriazine di-N-oxides", pages 977-981) See RN 121135-27-1, 121135-28-2, 121135-30-6, 121140-01-0	64, 65

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/NZ03/00210

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	91/04028	AU	646794	DE	68929050	EP	478545
		JP	3034541	NO	920747		
EP	972517	AU	74117/94	CA	2132578	DE	69424915
		EP	649658	JP	7215882	RU	2148406
		US	5484612	US	5670502	US	6121263
		US	6277835				
US	5827850	AU	68548/96	AU	69690/98	CA	2232989
		CN	1202827	EP	866709	EP	1044005
		JP	11511479	JP	2001523248	RU	2166946
		US	6153610	WO	9711699	WO	9847512
DD	272591						

END OF ANNEX

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